1978

Part I. Synthesis of oxygenated derivatives of dibenzo-[b,d]pyran-6-one as precursors for lycorine- and crinine-type alkaloids; Part II. Modifications of crinine alkaloids for the synthesis of pretazettine and precriwelline

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Part I: Synthesis of oxygenated derivatives of dibenzo-[b,d]pyran-6-one as precursors for lycorine- and crinine-type alkaloids

Part II: Modifications of crinine alkaloids for the synthesis of pretazettine and precriwelline

by

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PART I: SYNTHESIS OF OXYGENATED DERIVATIVES OF DIBENZO[b,d]PYRAN-6-ONE AS PRECURSORS FOR LYCORINE- AND CRININE-TYPE ALKALOIDS

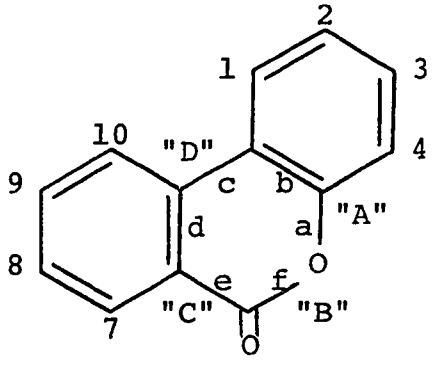
INTRODUCTION

The Amaryllidaceae alkaloids are among the few classes of alkaloids to contain the phenanthridine ring system. A short synthesis of this nucleus which included the functionality necessary for further transformations would greatly facilitate the synthesis of these alkaloids. Discussed in this dissertation are synthetic attempts at lycorane and crinane, two ring systems which are present in a very large proportion of the Amaryllidaceae alkaloids. Also discussed is an attempt to synthesize narciprimine, an amide which is also found in Amaryllidaceae plants.

HISTORICAL

Dibenzo[b,d]pyran-6-one and its Derivatives

Dibenzo[b,d]pyran-6-one (1) and its derivatives have been synthesized by a number of fundamentally different routes. It will be convenient for the purposes of this dissertation to refer to these conceptually different approaches as type "A" through type "D". A type "A" synthesis would involve formation of bond "A" in 1 as the most important step in the sequence. A type "B" synthesis would indicate that bond "B" is formed in the most important step and so on. The symbols "A" and "B" should not be confused with the small letters that are used to name the ring system.



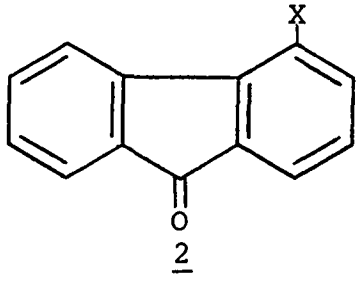
1

Type "A" syntheses generally proceed by a free radical process or by nucleophilic aromatic substitution. Typically, the alkali metal salt of biphenyl-2-carboxylic acid, or of diphenic acid, is treated with an oxidizing agent.

Diphenic acid loses carbon dioxide prior to cyclization. Oxidizing agents that have been tried include hydrogen peroxide (1), lead tetraacetate (2), chromium trioxide (3), and persulfate (4). Investigations using these oxidants were prompted by reports in the early 1960's of dibenzo[b,d]-pyran-6-one formation by thermal decomposition of dibenzoyl peroxide (5) and di-2-phenylbenzoyl peroxide (6).

2'-Nitrobiphenyl-2-carboxylic acid, as its potassium, quinoline or piperidine salt, forms dibenzo[b,d]pyran-6-one by intramolecular nucleophillic displacement of the nitro group by the carboxylate ion upon heating (7).

Type "B" syntheses are characterized by ring expansion of fluorenones. In one of the first dibenzo[b,d]pyran-6-one syntheses 4-hydroxy-9-fluorenone (2a) was treated with potassium hydroxide. Ketonic cleavage, rotation about the phenyl-phenyl bond and lactonization provided the desired product (8). In addition, 4-amino-9-fluorenone (2b) gave the corresponding lactam (8).



2

a) X = OH

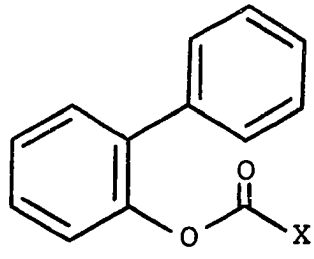
b) X = NH_2

c) X = H

Baeyer-Villager oxidation of 9-fluorenone itself (2c) using hydrogen peroxide has proven effective in obtaining

high yields of pyrone (1). With 9-fluorenone, oxidation gave yields of 80% (9) and 85% (10) with 90% hydrogen peroxide and 30% hydrogen peroxide, respectively. Both reactions were carried out in acidic media. Even higher yields were obtained when 2-carbomethoxybiphenyl-2'-carboxaldehyde was subjected to similar Baeyer-Villager conditions (11).

There are two Friedel-Crafts acylations (type "C") that have yielded the compound of interest. The chloroformate ester of 2-hydroxybiphenyl (3, X = Cl) was cyclized to the lactone in 95% yield using aluminum chloride in chlorobenzene at 80° to 100°C (12). Also ethyl, 2-hydroxybiphenyl carbonate (3, X = OCH_2CH_3) gave the same product upon photolysis (13).



3

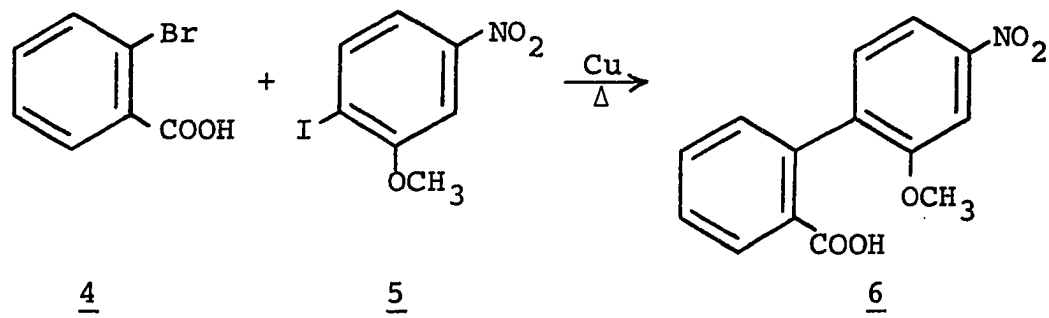
In what must also be classified as a type "C" synthesis Gilman et al. (14, 15) carbonated the lithio derivatives of both dibenzofuran and dibenzothiophene. Spontaneous lactonization gave the desired pyrone or thiopyrone. Dibenzopyrrole was also used as a substrate but did not give analogous results.

Most of the above procedures have started with a precursor which had an intact phenyl-phenyl bond. The final class of reactions (type "D") address the problem of formation of this biphenyl linkage. It may be argued that these syntheses are superior to those given previously for several reasons. First, biphenyls are neither inexpensive nor are they as available as monocyclic precursors. Second, substituents with which to elaborate the resultant pyrone are harder to introduce selectively into biphenyls. Third, some types of functionality are not compatible with the reaction conditions employed in syntheses of types "A", "B", and "C". The free radical reactions employ high temperatures and harsh oxidants. Type "B" reactions demand strong base or vigorous peracid oxidation and type "C" reactions employ strong Lewis acids or lithium metal. Although unsubstituted dibenzo-[b,d]pyran-6-one can withstand harsher reagents than functionalized pyrones, the following syntheses can be made milder to accommodate more sensitive functional groups. Often copper catalyses are responsible for this fortuitous result.

The earliest recorded synthesis of dibenzo[b,d]pyran-6-one was by Richter (16) in 1883. A mixture of sodium salicylate and phosphorous oxychloride was heated, evolved carbon dioxide, and resulted in poor yields of the pyrone. Though no mechanistic details were given, a 1971 synthesis

involving pyrolysis of potassium-o-iodobenzoate (17) must be similar. Both are probably an Ullmann-type coupling followed by oxidative loss of carbon dioxide and ring closure. Thus this reaction is a combination of a type "D" and a type "A" synthesis.

In 1960 3-nitrodibenzo[b,d]pyran-6-one was made by coupling o-bromobenzoic acid (4) and 2-iodo-5-nitro anisole (5) using a copper catalyzed Ullmann reaction to give 6. Acid cleavage of the methyl ether resulted in lactonization of the biphenyl (6) to the nitropyrone. This product was elaborated through its diazonium salt to further derivatives (18).



4 5 6

Other substituted dibenzopyrones were made by a similar method in 1973 (19). Ullmann coupling using 4 with other iodobenzenes and internal Friedel-Crafts cyclization gave a fluorenone derivative which was oxidized in a Baeyer-Villager fashion to give the desired products. Most of these derivatives were methoxy-substituted pyrones.

Diazonium salts have also been exploited in type "D" syntheses. Anthranilic acid was diazotized with amyl nitrite, then heated in the presence of phenol and a catalytic amount of copper metal. Both ortho and para coupling were observed. The ortho product spontaneously lactonized to the desired pyrone (20).

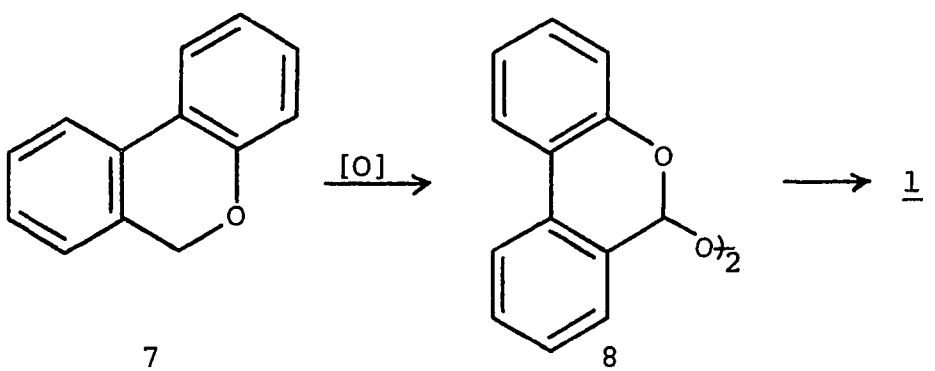
In 1975 another free radical process was discovered. Sodium benzoate was oxidized in a two phase system which included copper salts and ammonium thiosulphate in water-benzene-acetonitrile (21). The benzoate ion was oxidatively cleaved to form carbon dioxide and a phenyl radical. The radical attacked starting material to give isomeric biphenyl carboxylates. The ortho isomer further reacted by forming a carboxyl radical which cyclized in a type "A" manner to give the product.

Many of the above type "D" reactions either are not regiospecific when dealing with substituted pyrones or result in lower yields due to the formation of side products which cannot react further. For example, in the above two processes only the ortho coupled product was capable of further reaction to the cyclized pyrone. In addition, Baeyer-Villager oxidations can conceivably go in either or both of two directions.

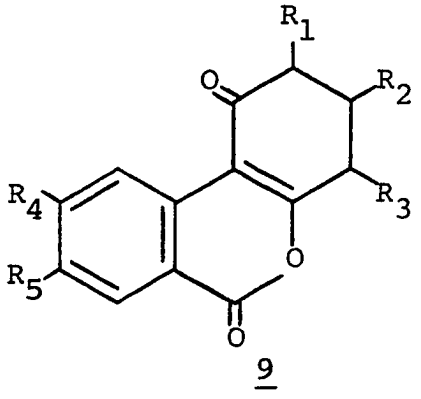
In 1929 Hurtley (22) introduced an experimentally easy, totally regiospecific process for the synthesis of

dibenzo[b,d]pyran-6-one. He also laid the ground-work for the eventual synthesis of 1-keto-1,2,3,4-tetrahydrodibenzo[b,d]pyran-6-ones. The reaction involves heating an aqueous solution of sodium o-bromobenzoate with the monosodium salt of resorcinol in the presence of a catalytic amount of a copper(II) salt. Upon filtration, a good yield of 3-hydroxydibenzo[b,d]pyran-6-one is obtained. Hurtley also found that o-bromobenzoic acid and active methylene compounds underwent a similar copper catalyzed condensation in alkaline media. Adams et al. (23) capitalized on this work in his synthetic efforts directed towards the synthesis of cannabinols. The alkaline condensation with resorcinol and other m-dihydroxybenzenes was studied in more detail by Devlin (24) in 1975.

Dibenzo[b,d]pyran-6-one has also been found in very small amounts in the residues of phenanthrene and anthracene oxidations (25) and from copper catalyzed decarboxylations of coal products (26). Finally, the pyrone has been made by oxidation of the 6-H-pyran (7) through the peroxide (8) (27).

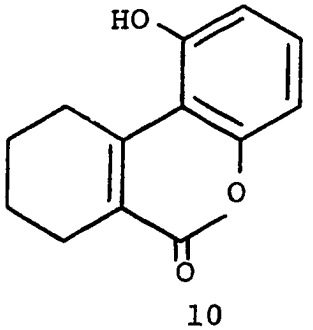


The synthetically more useful tetrahydrodibenzo[b,d]-pyran-6-ones have a less prolific history. Adams, following Hurtley's lead with active methylene compounds, condensed o-bromobenzoic acids with cyclohexane-1,3-diones to give 1-keto-1,2,3,4-tetrahydrodibenzo[b,d]pyran-6-one (9a) and some derivatives. His exploration, however, was not exhaustive as he confined himself to the synthesis of derivatives that would be important to his synthetic work on cannabinols. This work will be discussed in detail later. Adams also developed a procedure for obtaining 1-hydroxy-7,8,9,10-tetrahydro derivatives of the pyrone (10). This process involved heating resorcinol and ethyl cyclohexanone-2-carboxylate in phosphorous oxychloride.



9

	R_1	R_2	R_3	R_4	R_5
a)	H	H	H	H	H
b)	H	nC_5H_{11}	H	CH_3	H
c)	H	H	CH_3	H	H
d)	CH_3	H	H	H	H
e)	H	H	H	(OCH_2O)	
f)	H	H	R	(OCH_2O)	

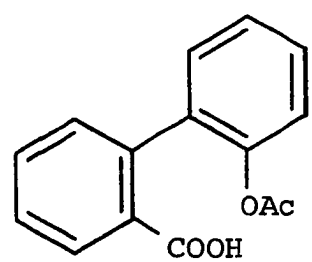


10

Dibenzo[b,d]pyran-6-one has been screened for a number of possible uses. It has not, however, found widespread acceptance in any of them. Some of its properties include biological activity against rodents (1) and microorganisms (28). U.S. Steel justified research on dibenzopyrones by finding them to be rodent repellants. Meanwhile, Sun Oil Co. found it to be effective against the algae S. Obliquos, C. Vulgaris, A. Catenula and O. Borneti, the bacteria Proteus Vulgaris and Salmonella Typhimurium, and the yeasts Candida Albicans and Saccharomyces Cerevisiae. The pyrone was also effective in vitro in mice against C. Albicans and Pseudomonas Aeruginosa.

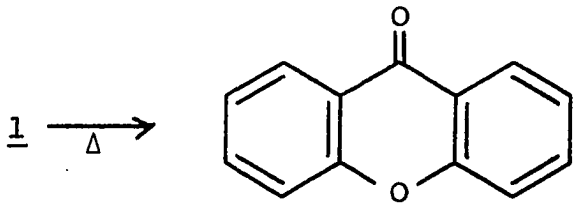
When tested as an analgesic dibenzo[b,d]pyran-6-one and some derivatives were found devoid of significant activity (29). The best result was found in 11 which was about half as active as aspirin probably due to the similarity it bears to acetylsalicyclic acid.

Gilman et al. (30) tested the pyrone (1) as a liquid scintillator solute but found it to be unsatisfactory.



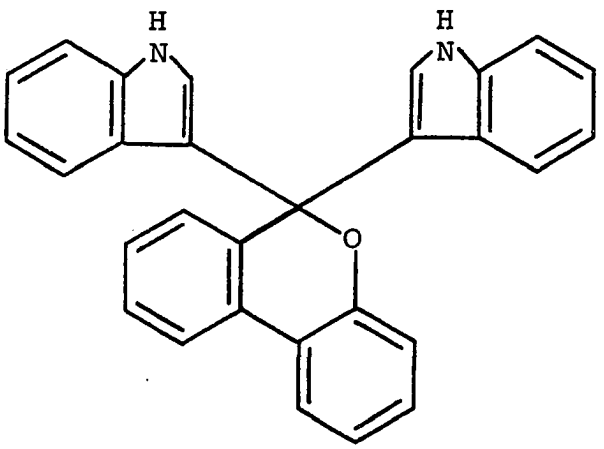
11

The most important industrial use of dibenzopyrones seems to be in the textile industry. When cloth or paper treated with 1 is heated to 125°C, the material becomes an effective ultraviolet screen (31). Chemically, this is achieved through thermal isomerization to xanthone (12). This diaryl ketone absorbs ultraviolet light more intensively than the lactone.



12

When dibenzo[b,d]pyran-6-one is treated with indole in the presence of phosphorous oxychloride and tin tetrachloride, an indicator dye (13) is formed (32).

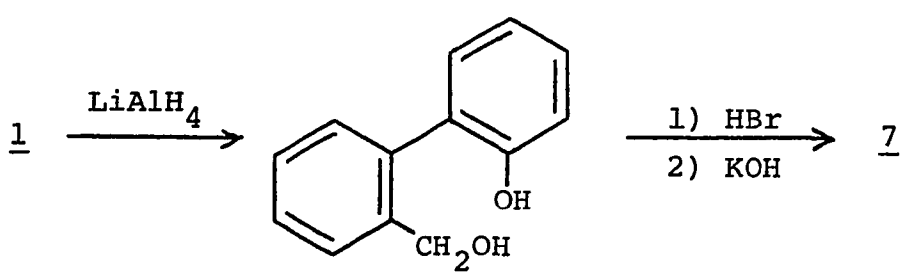


13

Compound 1 was also found to form a 2:1 adduct with tin tetrachloride in pentane (33). The complex precipitated from the hydrocarbon solvent and an elemental analysis was performed. No structural data was given. The complex formation property was not unique to dibenzopyrone but was observed for other lactones as well.

The type "A" formation of 1 was utilized to study deuterium isotope effects (34). 2-(2-Deuteriophenyl)benzoyl peroxide was heated and the percent of the deuterium retained in the product was determined. Since there are two possible sites of proton extraction and cyclization the extent of the competition between hydrogen and deuterium extraction could be observed. The resultant molecules would be either labeled in the C-1 position or would be unlabelled. The isotope effect actually observed was 1.32.

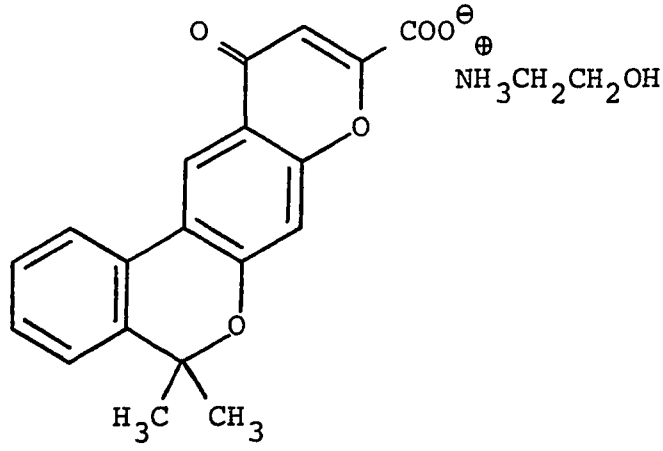
The chemistry of dibenzo[b,d]pyran-6-one is limited. Japanese workers performed a lithium aluminum hydride reduction of 1 in THF and obtained the expected diol 14 (35).



14

The diol (14) was subsequently converted to the 6-H-pyran 7 in two steps. Hydrogen bromide converted 14 to the benzyl bromide which was cyclized by an internal Williamson ether synthesis using potassium hydroxide.

The conversion of 1 to 7 was accomplished much more efficiently and without ring cleavage in one step by Devlin (24). Devlin found that this reduction took place with ease using the combination of boron trifluoride etherate and sodium borohydride (diborane). Devlin's work was aimed at the synthesis of a new class of drugs for the treatment of allergic reactions (36). After a few modifications of the dibenzopyrone nucleus, a molecule was found that prevented the release of histamine in monkey lung tissue. The compound (15) works against allergic attacks by preventing immediate hypersensitivity reactions.

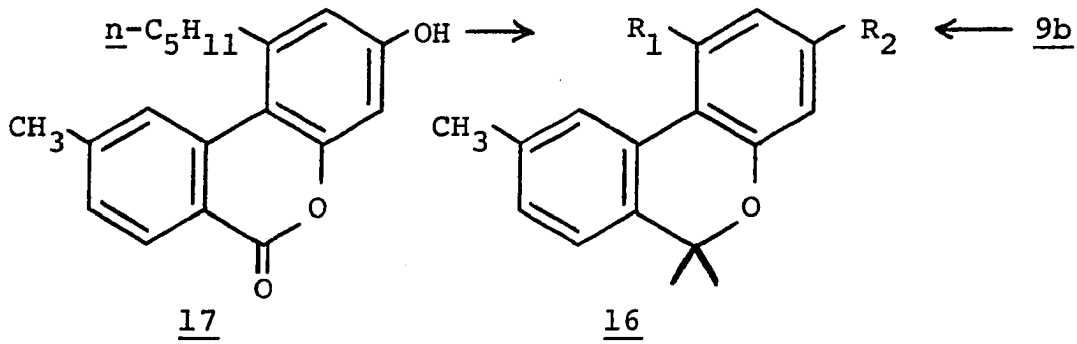


15

The 5,5-dimethyl moiety was introduced by the reaction of the lactone with two equivalents of methyl magnesium iodide. This reaction was first utilized on 1 and its derivatives by Adams in his structure proof of the cannabinols.

In the 1940's the structure of cannabinol, obtained from Wild Red Hemp (Cannabis sativa), was in dispute. Adams set out to prove the structure by synthesis (37-40). Structure 16 in which the relative positions of the n-amyl and hydroxyl groups was in question was proposed for cannabinol (37). Adams synthesized 16a by first condensing 2-bromo-4-methylbenzoic acid with olivetol (5-n-amyl resorcinol) by Hurtley's copper catalyzed procedure. The product (17) was treated with methyl magnesium iodide to obtain the ether 16a. By comparing the physical properties of the natural versus the synthetic materials it was found that 16a was not the correct isomer (37). Adams then synthesized 16b by condensing the same bromoacid as above with dihydroolivetol thus expanding upon Hurtley's choice of active methylene compounds by using a cyclic diketone (39). The product (9b) differs from the product of the condensation using aromatic precursors in the placement of the oxygen functionality relative to the A ring. This prompted Adams to investigate all of the possible isomeric methyl resorcinols (38) and dihydromethyl resorcinols (40)

regarding their behavior in the copper catalyzed reaction with o-bromobenzoic acids. He concluded that the diketone precursors all condensed at the 2-position and that the aromatic resorcinols condensed at the 4-position. Compound 9b was treated with methyl magnesium iodide followed by aromatization of ring C using palladium-on-charcoal to give 16b. Adams showed this to be identical with naturally occurring cannabinol.



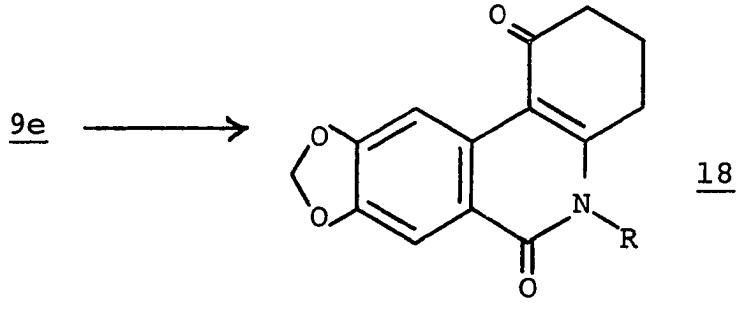
17 16

a) R_2 = OH R_1 = n-C_5H_{11}

b) R_2 = n-C_5H_{11} R_1 = OH

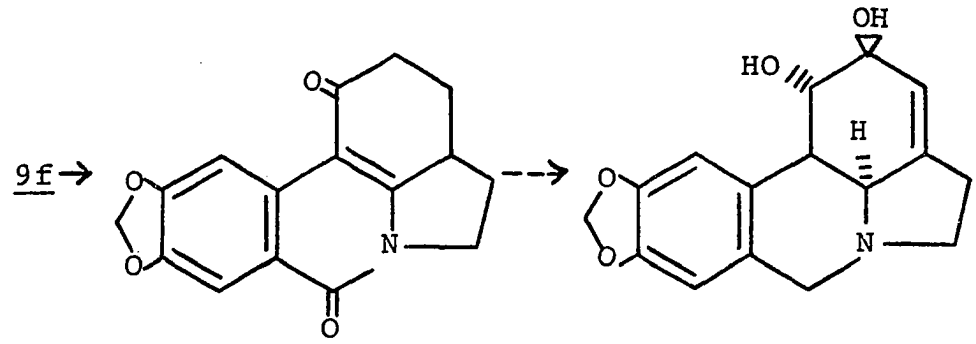
During his investigation of the condensation of dihydroresorcinols Adams found that when 3-alkyldihydroresorcinols were used, two products resulted. Isomers 9c and 9d are interconvertible through an equilibrium using methanolic potassium hydroxide. The lactone ring is cleaved, rotation occurs about the phenyl-cyclohexyl bond and the tautomerized intermediate recyclizes to give the rearranged compound (40).

Compounds 9a-f are all vinylogous anhydrides and as such will react easily with primary amines to form the corresponding imides. For example, 9e will react with ethylamine in refluxing ethanol to yield 18 (R = ethyl). Compound 18 (R = ethyl) was used by Fales et al. (41) as a model compound in ultraviolet spectral studies of oxidation products of the major Amaryllidaceae alkaloid, lycorine, (20).



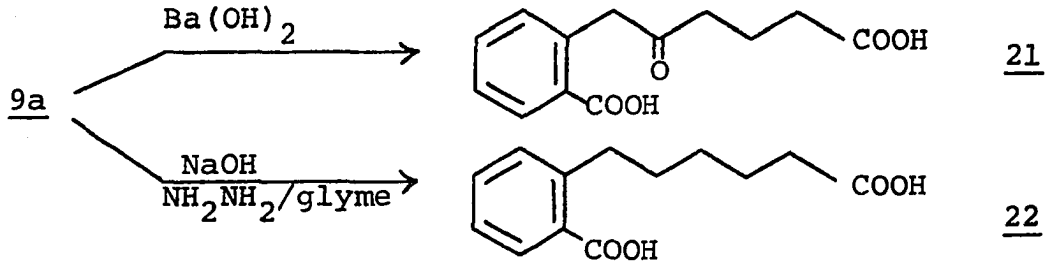
Wildman (42), combining the ideas inherent in the 9c and 9d equilibrium and in the facile formation of imides, proposed a short synthesis of the lycorine ring system. A compound such as 9f could be altered to include a primary amine on the side chain of the C ring. Internal imide formation would give the lycorine ring skeleton in just two steps from monocyclic precursors. Unfortunately, this reaction sequence could not be carried out probably due to steric constraints on the system as well as the aforementioned equilibrium, where 9d seems to be the favored isomer.

In 1955 German workers subjected 9c to Wolff-Kishner conditions and obtained two different diacids depending on



19 20

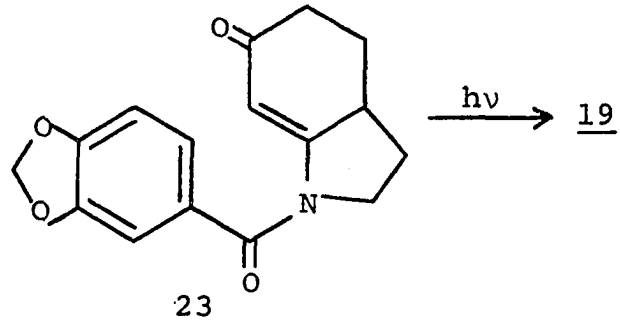
the variations used (43). Compounds 21 and 22 were obtained after acid hydrolysis.



21

22

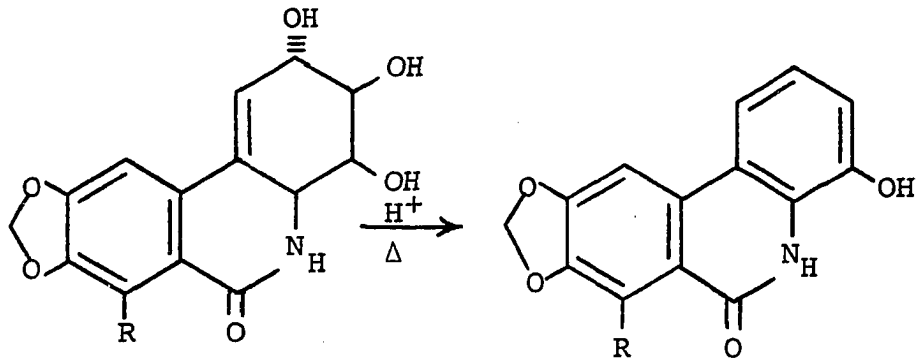
Compound 19 was made by Iida and coworkers (44) by a different route than has just been proposed. Compound 23 was prepared from piperonylyl chloride and the Birch reduction product of 6-methoxy-2,3-dihydroindole.



23 19

Photolysis of 23 gave 19 which was reduced with lithium aluminum hydride then reduced catalytically to give γ-lycorane.

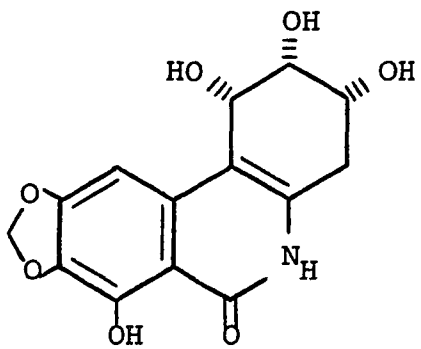
Aside from lycorane and cannabinol, the only other natural product synthesis that has been reported arising from the 1-oxo-1,2,3,4-tetrahydrodibenzo[b,d]pyran-6-one nucleus are the attempts at the Amaryllidaceae amides narciclasine (or lycoricidinol) (24, R = OH), lycoricidine (24, R = H) and narciprimine (25) (45).



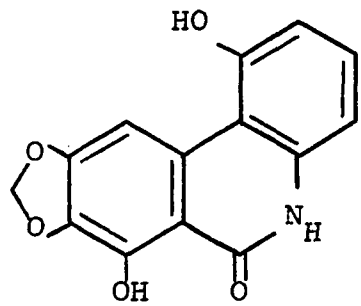
24 25

Some confusion as to the structure of 24 and 25 was at first experienced. Structure 26 was originally proposed for narciclasine based on NMR studies (46). This structure was proven to be incorrect by both chemical (47, 48), and X-ray crystallographic methods (49, 50). Narciprimine was also incorrectly assigned as structure 27.

Mondon and Krohn (51) synthesized isomer 27 and found it to be the wrong compound. Their synthesis was achieved



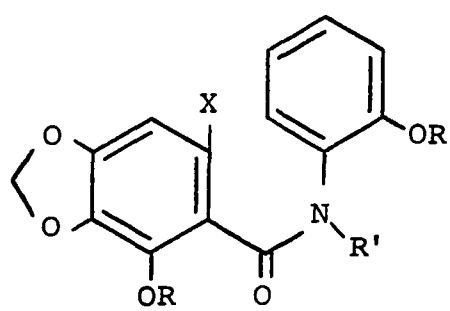
26



27

through the intermediacy of the 7-nitro-derivative of pyrone 9e. The nitro-derivative was converted via its diazonium salt to the 7-hydroxy-1-oxo pyrone then reacted with ammonia to form the imide which was aromatized with palladium-on-charcoal to provide 27.

The correct isomer of narciprimine, an artifact of narciclasine, was synthesized by two groups who both used type "D" syntheses. Savona and coworkers (47) cyclized compound 28a by a Pshorr reaction and Mondon and Krohn (48) followed a photochemical route utilizing 28b.



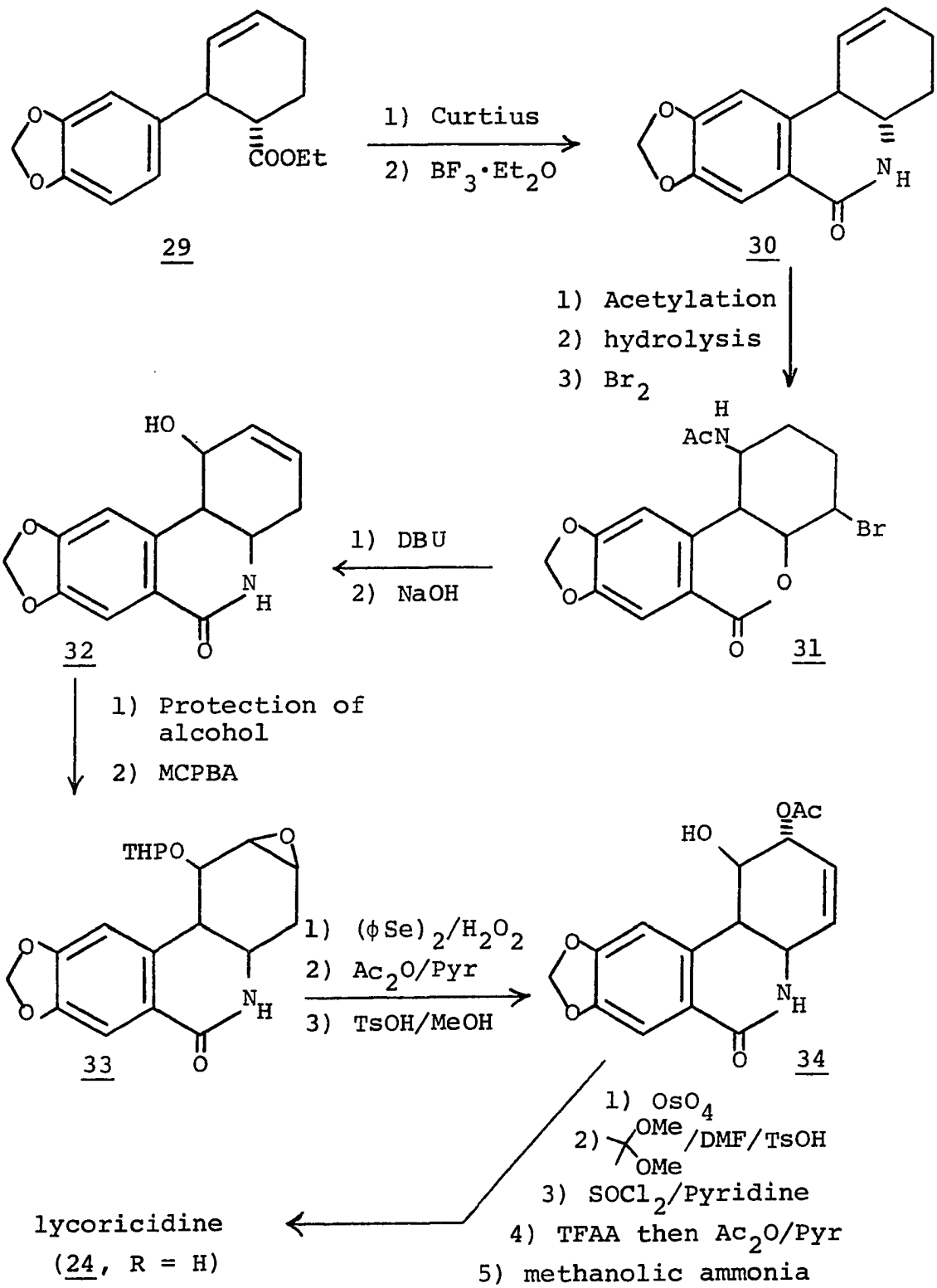
28

a) R = R' = CH_3; X = NH_2

b) R = Bz, R' = H; X = Br

Lycoricidine (24, R = H) has been synthesized by Japanese workers (52). The starting material for this synthesis (29) was made by a Diels-Alder reaction between ethyl acrylate and 1-(3,4-methylenedioxyphenyl)-butadiene. The synthesis is outlined in Scheme I. Compound 30 was made by subjecting 29 to a Curtius rearrangement then treating the isocyanate formed with boron trifluoride etherate. Acetylation of 30 was accomplished with refluxing acetic anhydride-pyridine. Basic hydrolysis gave a 68% yield of a carboxylic acid which, when treated with bromine, gave bromolactone 31. Dehydrohalogenation and basic hydrolysis gave 32. After protecting the alcohol as its tetrahydropyranyl ether, peracid oxidation of 32 gave 33. Compound 33 was treated with diphenyldiselenide and hydrogen peroxide. The olefinic diol monoether was acetylated and the THP protecting group removed using mild acidic conditions to afford olefinic diol monoacetate 34. Osmium tetroxide oxidation of the double bond followed by protection of the cis-diol as its acetonide gave an olefinic triol acetonide acetate after elimination of water using thionylchloride-pyridine. The conjugated olefinic triol triacetate was made from which lycoricidine could be obtained by using methanolic ammonia.

Scheme I


COOEt
1) Curtius
2) $BF_3 \cdot Et_2O$
29
30
1) Acetylation
2) hydrolysis
3) Br_2
HO
AcN
Br
1) DBU
2) NaOH
32
31
1) Protection of alcohol
2) MCPBA
THPO
1) $(\phi Se)_2/H_2O_2$
2) Ac_2O/Pyr
3) TsOH/MeOH
OAc
33
34
1) OsO_4
2) OMe, OMe /DMF/TsOH
3) $SOCl_2$/Pyridine
4) TFAA then Ac_2O/Pyr
5) methanolic ammonia
lycoricidine
(24, R = H)

RESULTS AND DISCUSSION

Oxygenated Derivatives of Dibenzo[b,d]pyran-6-one

The Amaryllidaceae alkaloids can all be viewed as derivatives of phenanthridine. Lycorine and crinine alkaloids contain the phenanthridine nucleus and the other families of alkaloids, lycorenine, tazettine and montanine, are rearranged products of these two basic ring skeletons. The amides narciclasine (24, R = OH), lycoricidine (24, R = H) and narciprimine (25) also contain the phenanthridine nucleus.

All of the above alkaloids, except narciclasine, have fallen to at least one successful synthesis, even though some may be formal syntheses. Each of them required elaborate multistep schemes in which the elegance of the synthesis was in doubt.

The copper catalyzed condensation of Hurtley (22) which was also used effectively by Adams and coworkers (37-39) and by Devlin (24) to construct dibenzopyrone seems an ideal reaction to apply to the synthesis of Amaryllidaceae alkaloids.

In an effort to find a shorter route to lycoricidine and narciclasine a number of experiments were run on the feasibility of using phenols other than resorcinol and phloroglucinol in the condensation with o-bromobenzoic acids. Unfortunately, excepting the above two phenols, none of the mono-, di-, or tri-hydroxybenzenes could be made to condense

with o-bromobenzoic acid. In the hope that a nitrogen analog of resorcinol would afford a lactam, m-phenylenediamine, m-aminophenol and 2,4-diaminophenol were used as substrates in the reaction. This tactic also proved fruitless.

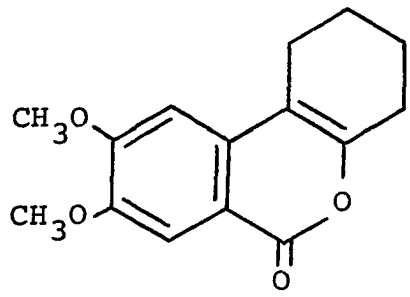
The idea of using aromatic precursors was then abandoned and, instead, the active methylenes were employed. One active methylene compound which had not been tried by Hurtley was nitromethane. Although the acidity of the methyl hydrogens in nitromethane is comparable to the compounds used by Hurtley, it did not give a product.

Dihydroresorcinol, originally employed by Adams, gave good results and was used to make the methylenedioxy ketolactone 9e. This compound provided a starting point for the major part of this dissertation.

Reactions of 1-Oxo-1,2,3,4-tetrahydro-8,9-methylenedioxy-dibenzo[b,d]pyran-6-one

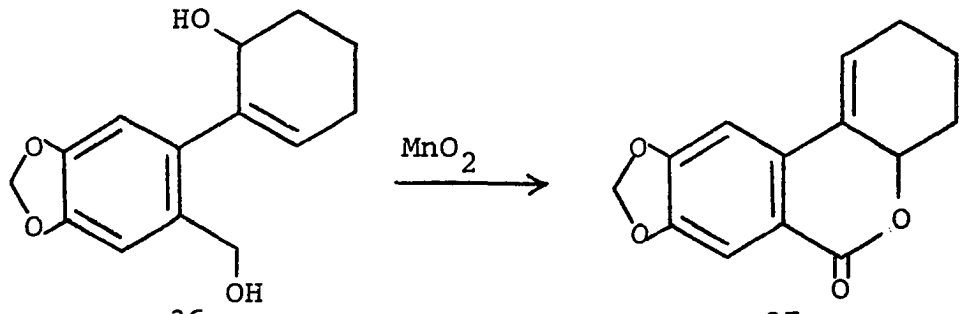
In an effort to devise a synthetic scheme aimed at lycorine the chemistry of the dimethoxy analog of 9e was explored. Reduction of the vinylogous anhydride with zinc powder in boiling acetic acid resulted in the loss of the 1-oxo group and produced 35.

More vigorous reduction with lithium aluminum hydride in refluxing ether for three days gave a compound which gave a diacetate upon acetylation and whose ultraviolet spectrum indicated a styrene-type compound. Based on



35

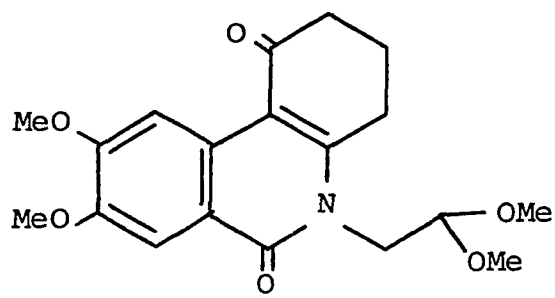
infrared and nuclear magnetic resonance spectra structure 36 is proposed. Additionally, if 36 is oxidized with manganese dioxide the lactone 37 is produced.



36 37

Pyrone 9e, as an anhydride, reacts readily with primary amines to form imides. The simple primary amines ethyl, isopropyl and tert-butyl amine provided the corresponding imides in acceptable yields. In order to obtain the functionality required for further manipulation to lycorine a variety of substituted amines were condensed with the pyrone. Ethanolamine readily gave an 80% yield of imide but, unfortunately, glycine ethyl ester failed to give a product.

This is due to the rapid reaction of the amino acid ester with itself to form a diketopiperazine in basic media. Tosylation of the alcohol function of the ethanolamine adduct had been accomplished previously but cyclization of this compound to the lycorine ring system had proved futile (42). For this reason another functional group was desired at the terminus of the amine side chain. An excellent choice of a functionalized primary amine that served this purpose was aminoacetaldehyde dimethylacetal. Reaction of this protected amino aldehyde with the pyrone gave an 85% yield of imide 38.

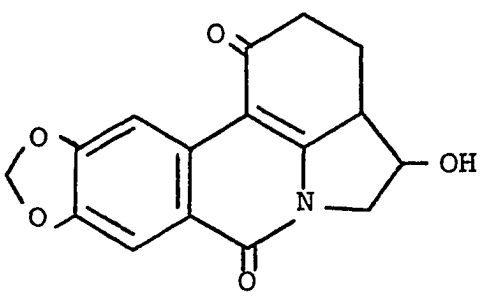


38

The synthetic strategy at this point was to regenerate the aldehyde and perform an aldol condensation between the aldehyde and the 4-position of the C-ring. This would give the lycorine skeleton in just three steps from monocyclic precursors.

The hydrolysis of the acetal proved more difficult than was at first suspected. Boiling 10% hydrochloric acid was required. After allowing the homogeneous mixture to cool

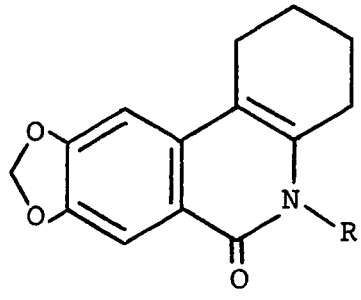
overnight, colorless crystals were observed. Infrared and nuclear magnetic resonance spectra both showed that no aldehyde had been formed in the reaction. A hydroxyl group was plainly evident in the infrared spectrum. At this time it was thought that the aldol reaction had already proceeded to give the lycorine skeleton 39 but no evidence for this structure has been found. Instead, it was postulated that the hydrate of the aldehyde had been formed and that this was the molecule giving rise to the spectral evidence presented. The mass spectrum of the compound indicated the presence of an aldehyde as there was a large m-1 peak and a m-28 peak. Furthermore, when the acetal (38) was treated with an acidic solution of 2,4-dinitrophenylhydrazine the yellow 2,4-dinitrophenylhydrazone characteristic of an aldehyde was obtained.



39

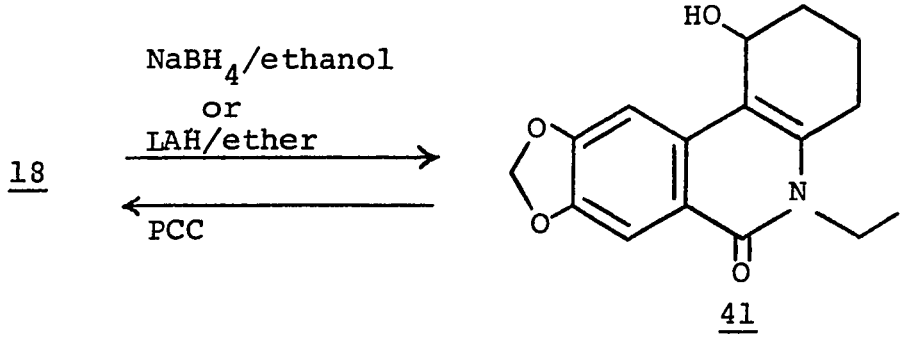
When the acetal (38) was reduced in zinc and acetic acid, the lactam 40 (R = H) was formed. The same reduction conditions, applied to the unsubstituted N-ethyl oxolactam (18, R = ethyl) gave a product that did not lose the amine

side chain (40, R = ethyl). The reason for this difference in product formation is that compound 38 is, in effect, an alpha substituted aldehyde. Zinc and acid reductions usually result in the cleavage of heteroatoms alpha to a carbonyl.



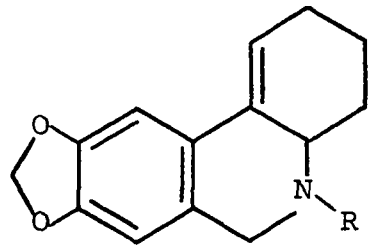
40

More vigorous reduction of the oxo lactams was undertaken. Compound 18 was reduced with lithium aluminum hydride in diethyl ether to yield the 1-hydroxylactam 41. Compound 41 was also produced by reduction of the same oxolactam with sodium borohydride in ethanol. Compound (18, R = ethyl) could be regenerated by oxidation of the alcohol with pyridinum chlorochromate. The chromium reagent was tried after it was found that manganese dioxide failed to oxidize the allylic alcohol.



41

Changing the solvent in the lithium aluminum hydride reduction from ethyl ether to tetrahydrofuran gave a more completely reduced product. This reduction provided the originally expected product 42 (R = ethyl) in 60% yield.

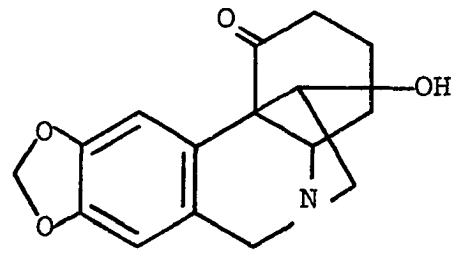


42

Armed with this information, the acetal (38) was reduced with lithium aluminum hydride in tetrahydrofuran under refluxing conditions. Results analogous to those obtained in the N-ethyl oxolactam reduction were realized. Compound 42 ($R = CH_2CH(OMe)_2$) was generated in excellent yield. Interestingly, diethyl ether gave the same results as tetrahydrofuran as the solvent in this reduction.

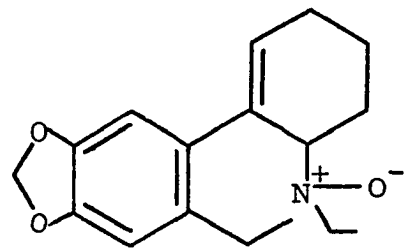
The results of these reductions and the inability to form compound 39 prompted a change in the goal of the synthesis. The chance of obtaining lycorine now seemed remote so the objective was revised to embrace the crinine ring system. The transformation of the olefin moiety in 42 ($R = CH_2CH(OMe)_2$) to a ketone at C-1 would allow an aldol condensation to occur between the benzylic carbon alpha

to the ketone and the potential aldehydic carbon. Compound 43 would be the result.



43

Unfortunately the alkene to ketone transformation was not achieved. The first attempt consisted of epoxidation of the double bond followed by acidic rearrangement of the epoxide to the ketone. This approach failed when it was deduced that the only product formed in the epoxidation reaction with monoperphthalic acid was the N-oxide 44.



44

Compound 44 was insoluble in most organic solvents and would not be oxidized further. Thus the experiment with the model compound showed that this approach was unfruitful.

The second approach involved hydroboration of the olefin. The organoborane thus formed could either be oxidized

directly to the ketone with chromic acid or first oxidized to the alcohol with hydrogen peroxide in base. The first alternative was rejected since the vigorous acidic conditions would undoubtedly cause the oxidation of the potential aldehyde. Mild peroxide treatment followed by separate oxidation to the ketone seemed a better course of action.

This approach also failed when the starting acetal (42, R = $CH_2CH(OMe)_2$) was recovered unchanged even after shaking the product in 10% hydrochloric acid. The stability of the acetal must be due to the fact that the amine is protonated in acid and the positive charge so near to the acetal discourages attack by another proton. The inability of diborane to effect a reaction was probably due to a coordination of the diborane to the amine. A repetition of this reaction should include the use of a larger excess of diborane.

SUMMARY

In order to find a shorter synthesis of narciclasine and narciprimine, all of the mono-, di-, and tri-hydroxy benzenes, as well as a few anilines and hydroxyanilines were subjected to the copper catalyzed condensation conditions of Hurtley using o-bromobenzoic acid. Only resorcinol and phloroglucinol were found to react.

In an effort to find a short route to lycorine and crinine alkaloids the chemistry of pyrone 9e was studied. Special consideration was given to the reduction of the pyrone. It was also found that the pyrone, a vinylogous anhydride, reacted with a variety of primary amines to give the corresponding imides. The chemistry of the imide formed from aminoacetaldehyde dimethylacetal was studied in detail with respect to hydrolysis of the acetal function, reaction with various reducing agents, and transformations of some of the reduction products. No complete synthetic scheme was found although the possibilities for further reactions have not been exhausted.

EXPERIMENTAL

Instrumentation

Melting points were taken on a Koffer hot stage microscope with polarizing filter and are corrected. Infrared spectra were run on a Beckman Model IR 4250 spectrometer in chloroform solution or in a potassium bromide pellet. Ultraviolet-visible spectra were obtained on a Cary Model 14 spectrophotometer in 95% ethanol solution through quartz cuvettes. 60 MHz proton magnetic resonance spectra were run on either a Hitachi Perkin-Elmer Model R-20B, Varian Model A-60 or a Varian EM 360. 100 MHz spectra were obtained on a Varian Model HA-100. All chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were run on a A.E.I. MS 902 high resolution mass spectrometer. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tennessee.

Solvents and Reagents

Anhydrous ether was used directly from a freshly opened can. Tetrahydrofuran was distilled from lithium aluminum hydride immediately before use. Anhydrous ethanol and methanol were prepared by distilling from magnesium turnings and stored over 3 Å molecular sieves (Ventron-Alfa Products). Potassium carbonate was used for drying organic solvents (unless otherwise stated).

Obtained from the Aldrich Chemical Company were cyanogen bromide and cyclohexane-1,3-dione. These were used without further purification.

Synthetic Procedures

Condensation of o-bromobenzoic acid with selected phenols and anilines

Ten runs of this condensation were done in the same way. Two grams of sodium hydroxide (0.5 moles) and five grams of o-bromobenzoic acid (.025 moles) were dissolved in 50 ml of distilled water. To this solution was added .05 mole of the phenolic substance or aniline and the mixture heated on a hot plate to boiling. Two ml of a 10% solution of copper sulfate was added, the flask was allowed to cool slowly, and then the contents acidified with 25% hydrochloric acid. This mixture was brought to a pH of about 8 by the addition of sodium bicarbonate. The remaining solid in the solution was suction filtered and washed with water. The filter cake was then dried and recrystallized from acetone. Table 1 shows the phenols and anilines used and the weight representing .05 mole. As Table 1 shows, resorcinol and phloroglucinol were the only phenols to react. The products had melting points above 350°C and were not soluble enough in organic solvents for spectra to be taken. For this reason the acetates of these products were made as follows.

Table 1. Condensation of o-bromobenzoic acid with selected phenols and anilines

Compound	Amount (grams)	Reaction	NMR
phenol	4.7	none	---
catechol	5.5	none	---
resorcinol	5.5	yes[a]	Figure 1
hydroquinone	5.5	none	---
pyrogallol	6.3	none	---
hydroxyhydroquinone	6.3	none	---
phloroglucinol	6.3	yes[b]	Figure 1
m-aminophenol	5.45	none	---
m-phenylenediamine	5.4	none	---
2,4-dinitrophenol	6.2	none	---

[a]Acetate mp 174-175°C.

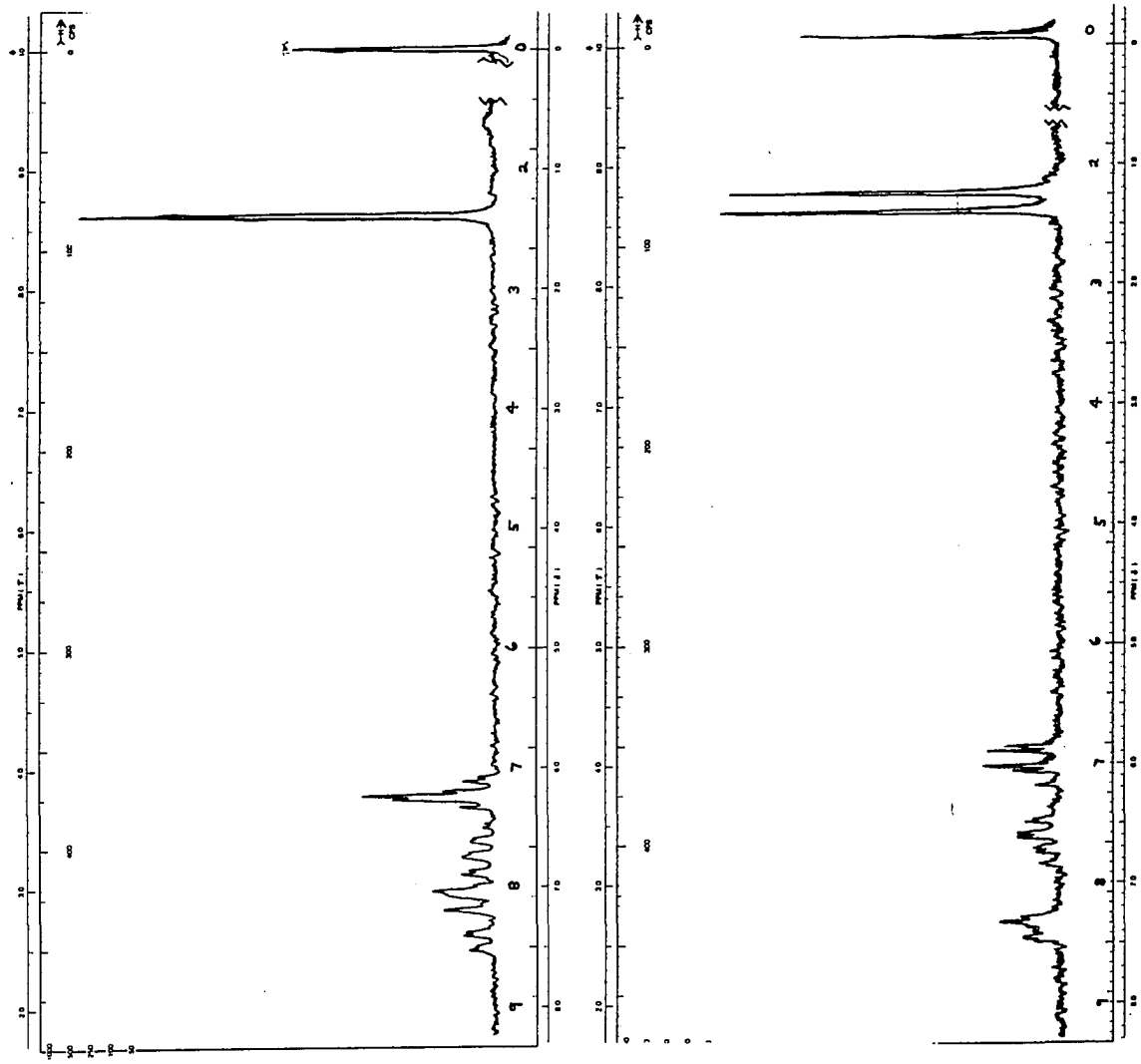
[b]Acetate mp 175-176°C.

Two grams of the dried benzocoumarin was dissolved in 25 ml of pyridine. Acetic anhydride (20 ml) was added which caused an immediate precipitate to form. This solid was filtered after 10 min and washed with water and dried. The crystals were recrystallized from toluene-acetone.

Choice of A-ring substitution

Most Amaryllidaceae alkaloids have been found to contain either a methylenedioxy group or two adjacent methoxyl groups on the A-ring of their molecules. At the start of the work on this dissertation precursors which had the dimethoxy

Figure 1. NMR spectra of acetyl-3-hydroxydibenzo[b,d]pyran-6-one and diacetyl-1,3-dihydroxydibenzo[b,d]pyran-6-one



substitution were used. As more starting material was needed it was thought that the methylenedioxy group would prove more useful in comparison of the synthetic materials to the natural alkaloids. Though both substitution patterns have been used, where duplication of molecular structures have occurred only the methylenedioxy intermediates have been shown.

Attempted condensation of nitromethane

5 g of o-bromobenzoic acid was dissolved in 1 g of NaOH in 15 ml of water. 3 g of nitromethane was added and the solution was heated. To the hot solution was added 2 ml of 10% copper sulfate. After 10 min, the solution was neutralized with dilute HCl and filtered. Complete acidification of the filtrate gave a brown precipitate. The melting point, infrared and nuclear magnetic resonance spectra showed that the material was the starting bromo acid.

1-Oxo-1,2,3,4-tetrahydro-8,9-methylenedioxydibenzo[b,d]pyran-6-one (9e)

The procedure of Fales, Warnhoff and Wildman (41) was used. Sodium (3.66 g) was dissolved in 100 ml of absolute ethanol. To this was added, in order of addition, 18.8 g of 6-bromopiperonylic acid, 10.5 g of cyclohexane-1,3-dione and .5 g of copper(II) acetate. The mixture was refluxed under a nitrogen atmosphere for six hours then poured into 300 ml

of cold water and extracted with chloroform. The organic layer was washed with saturated sodium bicarbonate then dried over $MgSO_4$. The solvent was removed in vacuo and the residue recrystallized from boiling acetone (450 ml). Yield 5.96 g (25%), mp 211-213°C, lit value (41), 211-213°C.

1,2,3,4-Tetrahydro-8,9-dimethoxydibenzo[b,d]pyran-6-one (35)

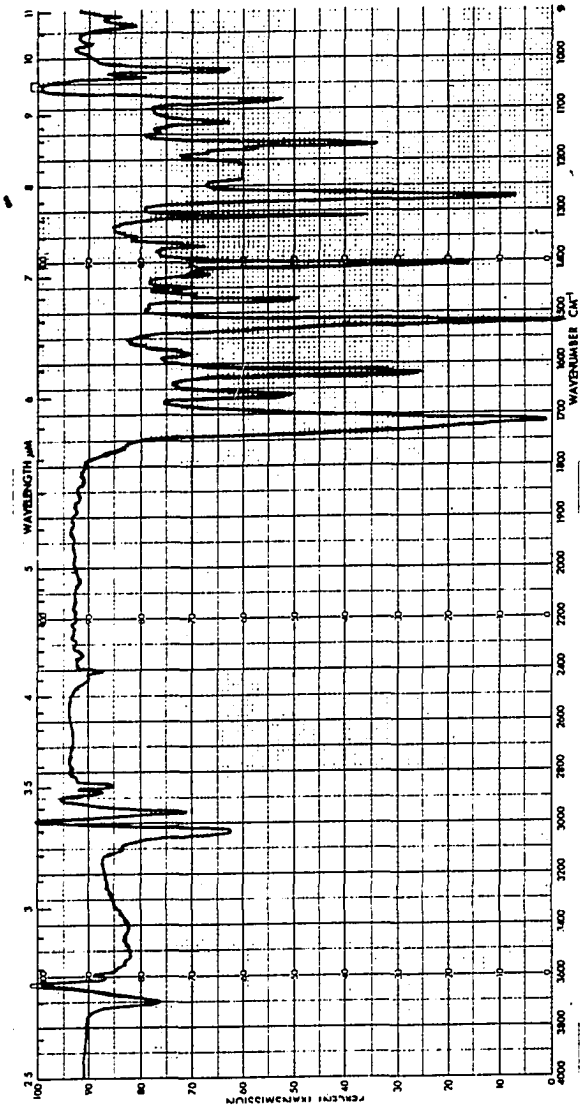
The oxopyrone 9 (200 mg) was dissolved in 200 ml of glacial acetic acid. Activated zinc powder (20 g) was added and the solution stirred magnetically while refluxing for 24 hours. The zinc metal had turned from dull gray to shiny. The hot solution was filtered and the filtrate was diluted with ether. This solution was washed with 5% sodium hydroxide solution and then with water. The ether layer was dried over magnesium sulfate and concentrated under reduced pressure to about 10 ml. After standing for five days, long pink needles were observed. Yield 50 mg (26%), mp 198-200°C.

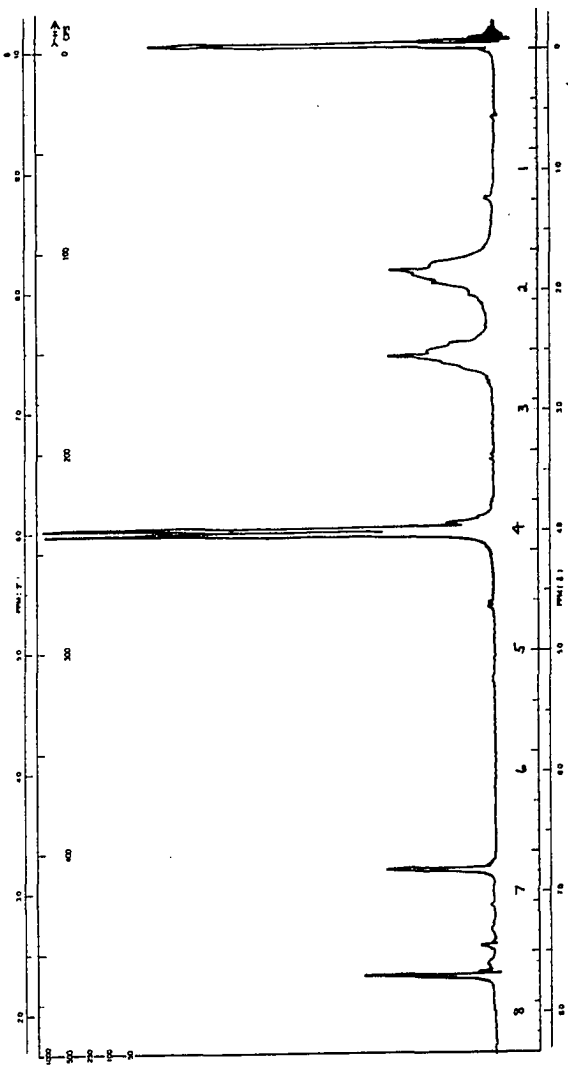
M.S. ($C_{15}H_{16}O_4$) calculated 260.08412
observed 260.09307

IR Figure 2 NMR Figure 2

UV λ_{max} 334 nm, log ε 3.53; λ_{max} 292 nm, log ε 3.61;
λ_{max} 281 nm, log ε 3.73; λ_{max} 271 nm, log ε 3.72;
λ_{max} 256 nm, log ε 4.14; λ_{max} 246 nm, log ε 4.40

Figure 2. IR and NMR spectra of 1,2,3,4-tetrahydro-8,9-dimethoxy-dibenzo-[b,d]pyran-6-one (35)


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION



Lithium aluminum hydride reduction of pyrone (9e)

Lithium aluminum hydride (1.5 g) was placed in a dry 250 ml round bottom flask and 200 ml of dry diethyl ether was added. The ether was refluxed through a Soxhlet Extractor containing 750 mg of the oxopyrone (9e). After three days of refluxing, there was a residue in the thimble. The melting point (208-9°C) confirmed the identity of the residue as undissolved pyrone. The excess reagent in the flask was destroyed by adding 1.5 ml of water, 4.5 ml of 5% NaOH and 1.5 ml of water. The grannular precipitate was filtered through Celite and the filtrate washed with 100 ml of 5% HCl solution. The ether layer was dried, filtered through cotton and evaporated to dryness to give 250 mg of a fluffy solid. The solid was crystallized from carbon tetrachloride-ether (32%) (56% taking into account the undissolved pyrone).

IR Figure 3 NMR Figure 3

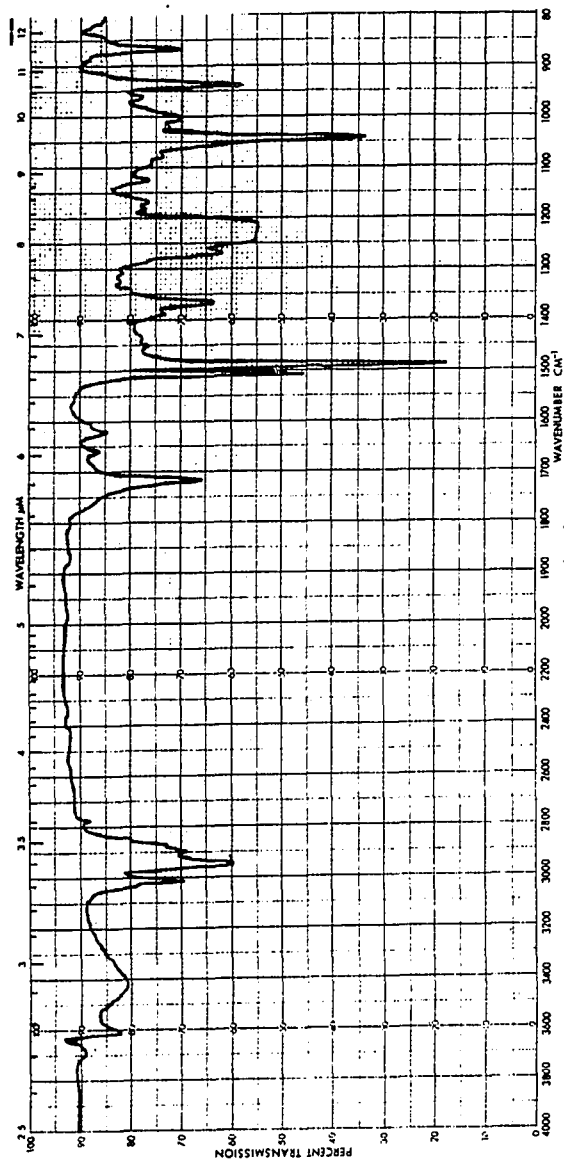
UV λ_{max} 290 nm, log ε 3.56; λ_{max} 241 nm, log ε 3.72

The acetate of the diol (34) was made from acetic anhydride in pyridine.

IR Figure 4 NMR Figure 4

The diol (34) (94 mg) was oxidized by 300 mg of manganese dioxide in 25 ml of chloroform. After 40 hours the mixture was filtered and purified by prep-scale TLC (silica gel; 3.5/.5; chloroform/ethyl acetate). The band at R_f .75 was

Figure 3. IR and NMR spectra of the lithium aluminum hydride reduction product of 1-oxo-1,2,3,4-tetrahydro-8,9-methylene-dioxydibenzo[b,d]pyran-6-one (36)


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION

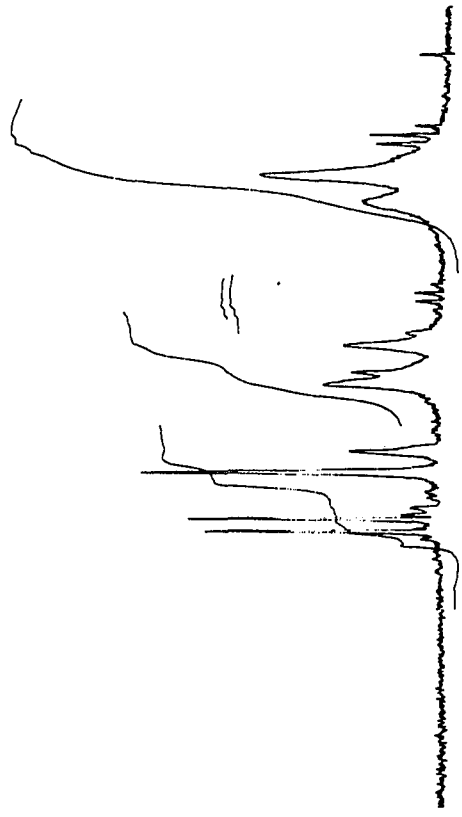
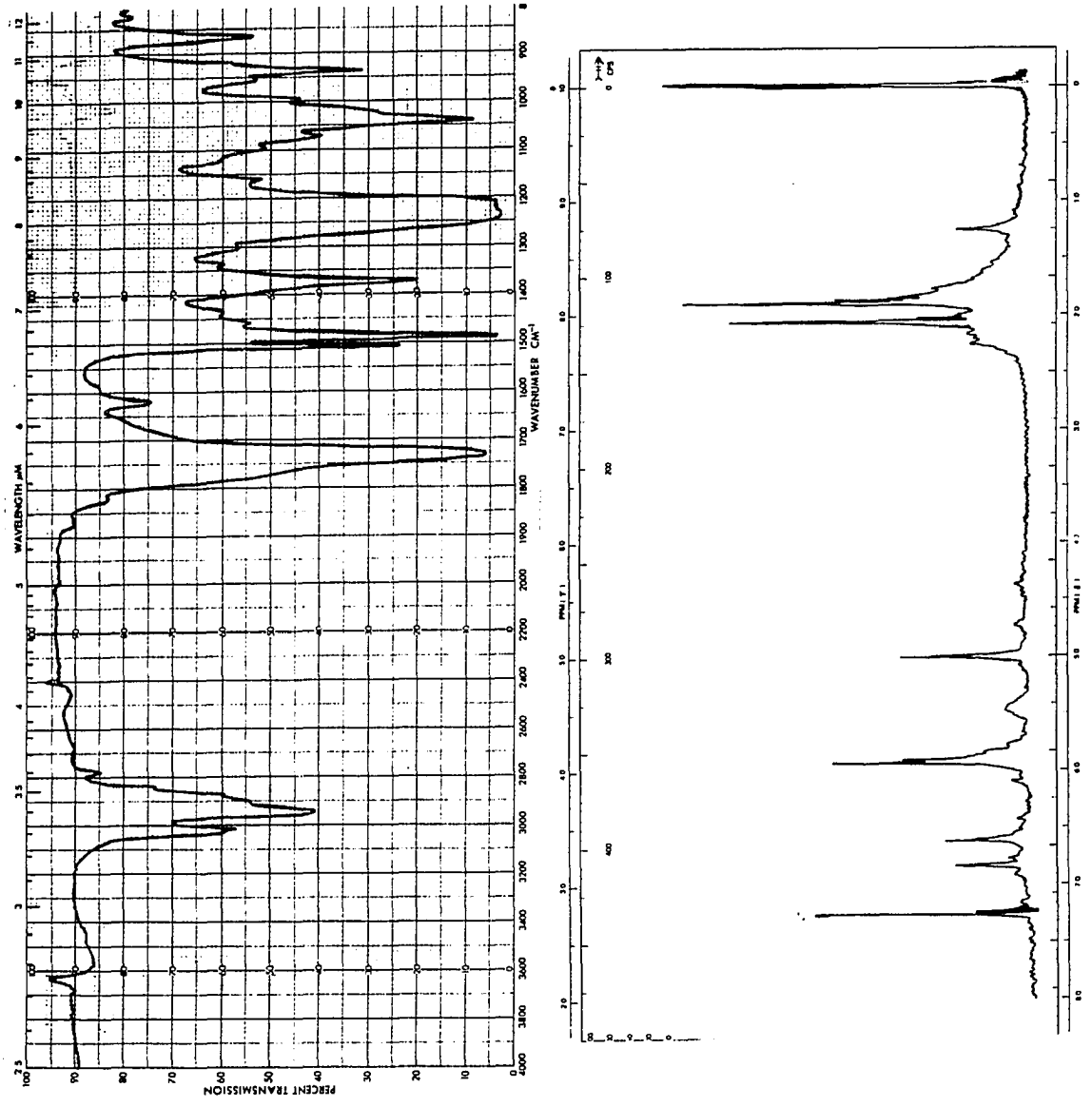


Figure 4. IR and NMR spectra of acetylation product of 36


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION

collected and identified as the lactone (37).

IR Figure 5 NMR Figure 5

UV λ_{max} 243 nm, log ε 4.46; λ_{max} 290 nm, log ε 4.00; λ_{max} 314 nm, log ε 3.90

N-Alkyl-1-oxo-1,2,3,4-tetrahydro-8,9-methylenedioxy phenanthridones (18)

These lactams were prepared according to the procedure of Fales, Warnhoff and Wildman (41). The oxopyrone (9e) was refluxed in an excess of the primary amine dissolved in enough absolute ethanol to dissolve the solid upon heating to boiling. After 3 hours to 3 days (see Table 2), the solution was allowed to cool to room temperature after clarification with Norite if necessary. The resultant crystals were suction filtered and air dried. The results are compiled in Table 2.

Acid hydrolysis of acetal (38)

This reaction was reproduced a number of times. The dimethoxy or methylenedioxy dimethyl acetal (37) was dissolved with heating in a minimum amount of 10% HCl. Upon cooling the reaction mixture overnight, crystals appeared which were insoluble in organic solvents (mp 233-235°C; 222-227°C, resp). The infrared spectrum showed both free and hydrogen bonded hydroxyl groups but no aliphatic aldehyde peak. The mass

Figure 5. IR and NMR spectra of manganese dioxide oxidation product of 36 (37)

PERCENT TRANSMISSION
WAVELENGTH μM
WAVENUMBER CM-1

Table 2. Reaction of primary amines with pyrone 9e

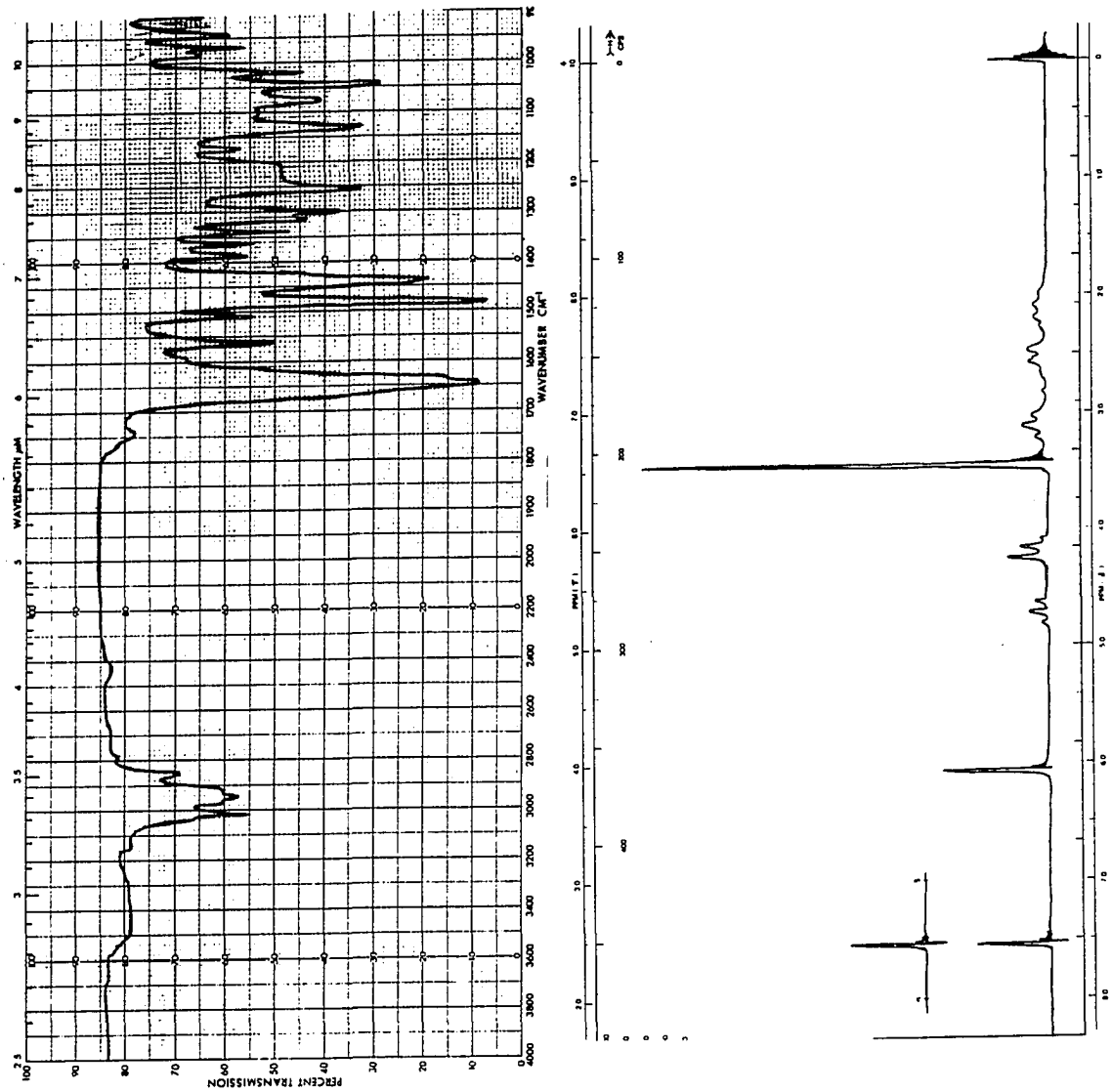
1° amine	Yield (%)	Reflux time (hrs)	mp°C	lit value (41)
ethyl amine	50	3	208-10	214-215
i-propyl amine	14	5	239.5-41.5	---
t-butyl amine	42	7.5	207-9.5	---
2-hydroxyethyl amine	81	3	215-216	---
glycine ethyl ester	0	72	no rxn	---
aniline	0	3	no rxn	---
aminoacetaldehyde dimethylacetal[a]	84	12	181-2	---
2,4-dinitrophenyl hydrazine[b]	low	0	268-272	---

[a]mp of dimethoxy analog 175-176°C. Elemental analysis of dimethoxy analog $C_{19}H_{23}NO_6$ requires C, 63.157; H, 6.371; N, 3.88; found C, 63.33; H, 6.71; N, 3.72. Elemental analysis of methylene dioxy analog $C_{18}H_{19}NO_6$ requires C, 62.609; H, 5.507; N, 4.058; found C, 62.48; H, 5.70; N, 3.96.

IR Figure 6 NMR Figure 6

[b]Dimethoxy analog.

Figure 6. IR and NMR spectra of N-(2,2-dimethoxy ethyl)-1-oxo-1,2,3,4-tetrahydro-8,9-methylenedioxy phenandridone (38)


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION

spectrum fragmentation suggested an aldehyde (m-1, m-18, m-28, m-48).

M.S. ($C_{16}H_{13}NO_5$) calculated 299.07938 (methylene dioxy)
measured 299.07944

IR Figure 7 (dimethoxy analog)

Reaction of hydrolysis product of acetal (38) with pyridine

In an attempt to acetylate the hydroxyl groups indicated by the infrared spectrum of the hydrolysis product of acetal 37, the compound was dissolved in pyridine and acetic anhydride added. Upon recovery of the product and characterization it was noticed that an aldehyde peak was now present in the NMR spectrum and a small aldehyde peak was found in the infrared spectrum. The same set of spectra were obtained when an attempted mesylation was tried. This suggested that the common solvent, pyridine, was changing the reactant and that the hydroxyl groups originally observed were due to hydration of the aldehyde group. Solution in pyridine generated the aldehyde mp 178-182°C.

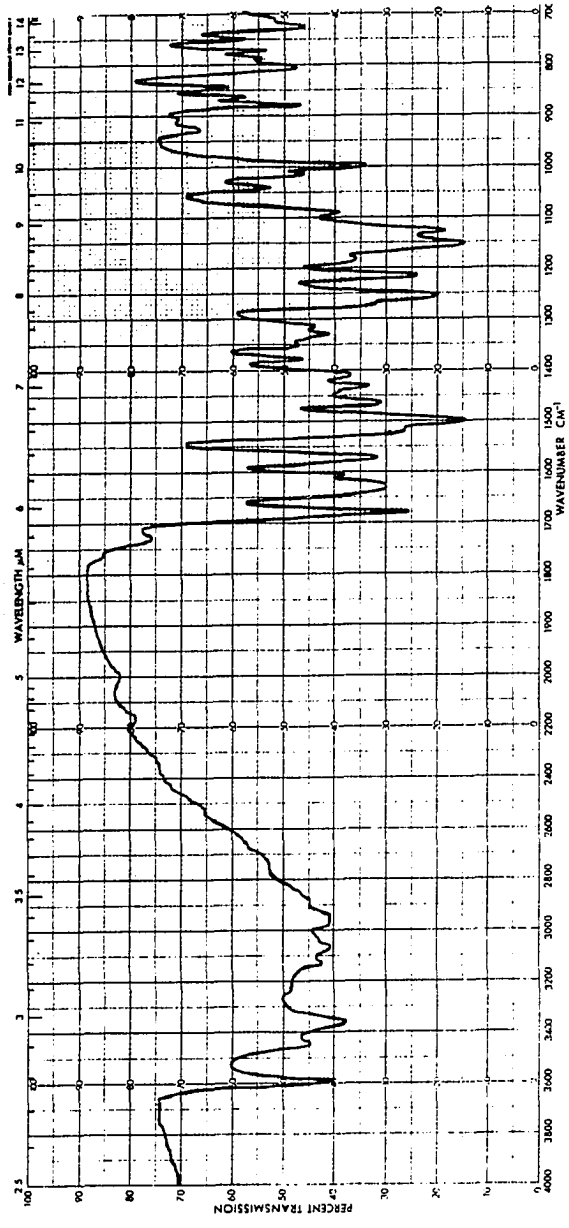
IR Figure 8 NMR Figure 8

If the aldehyde, formed from pyridine solution of the hydrate, was subjected to the hydrolysis conditions of the acetal (10% HCl), the hydrate was regenerated.

2,4-Dinitrophenyl hydrazine of the aldehyde

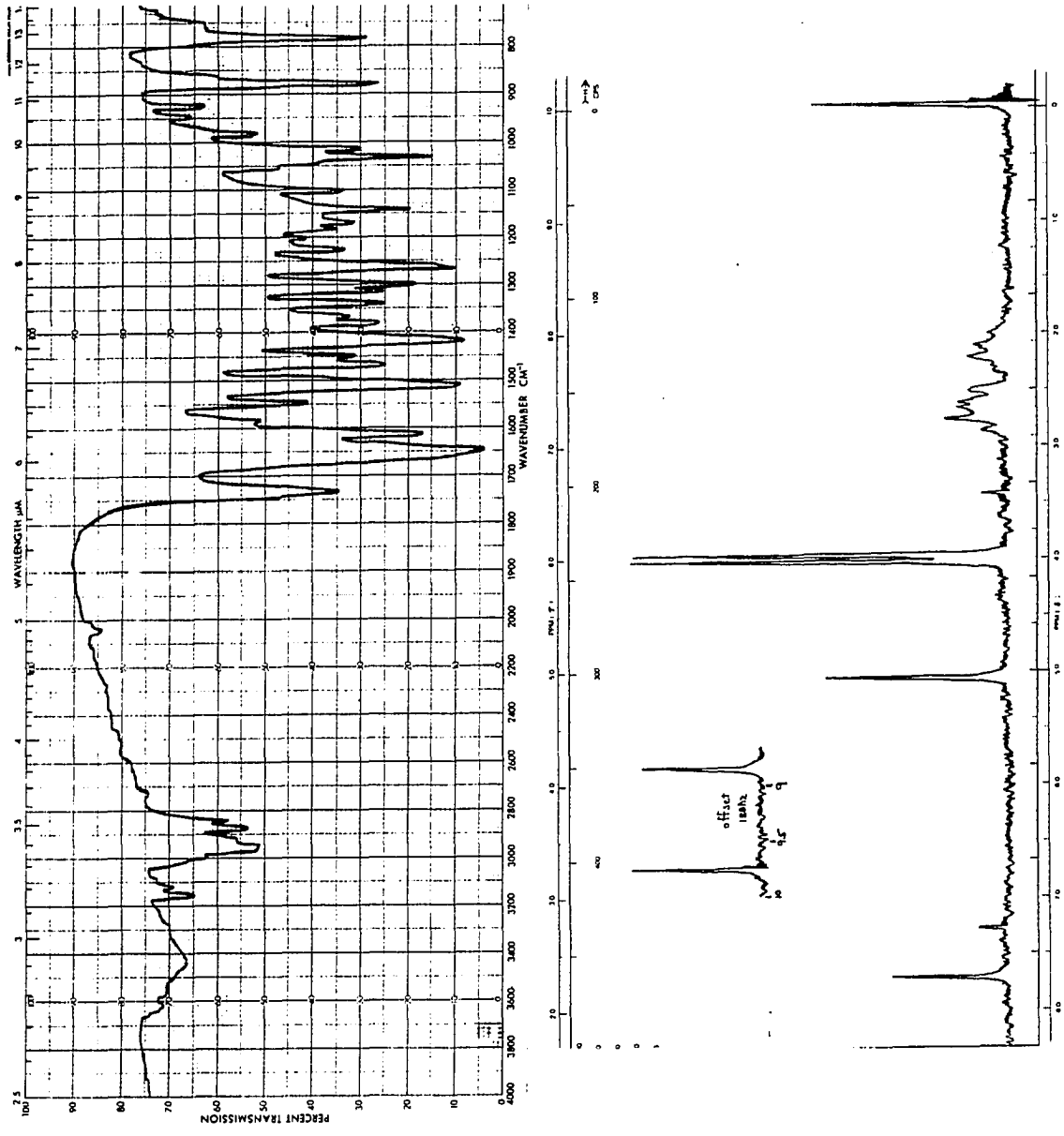
50 mg of acetal 37 was dissolved in 2 ml of hot 95% ethanol. To this was added 2 ml of a 2,4-dinitrophenyl

Figure 7. IR spectrum of acid hydrolysis product of 38 and UV spectrum of zinc/acetic acid reduction product of the acid hydrolysis product of 38


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION


210
230
250
270
290
310
330

Figure 8. IR and NMR spectra of the corresponding aldehyde of compound 38


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION

hydrazine solution in sulphuric acid and ethanol. The crystals were collected by centrifugation and recrystallized twice from hot ethyl acetate to yield yellow crystals mp 236-239°C.

N-ethyl-1,2,3,4-tetrahydro-8,9-dimethoxyphenanthridone (40, R = ethyl)

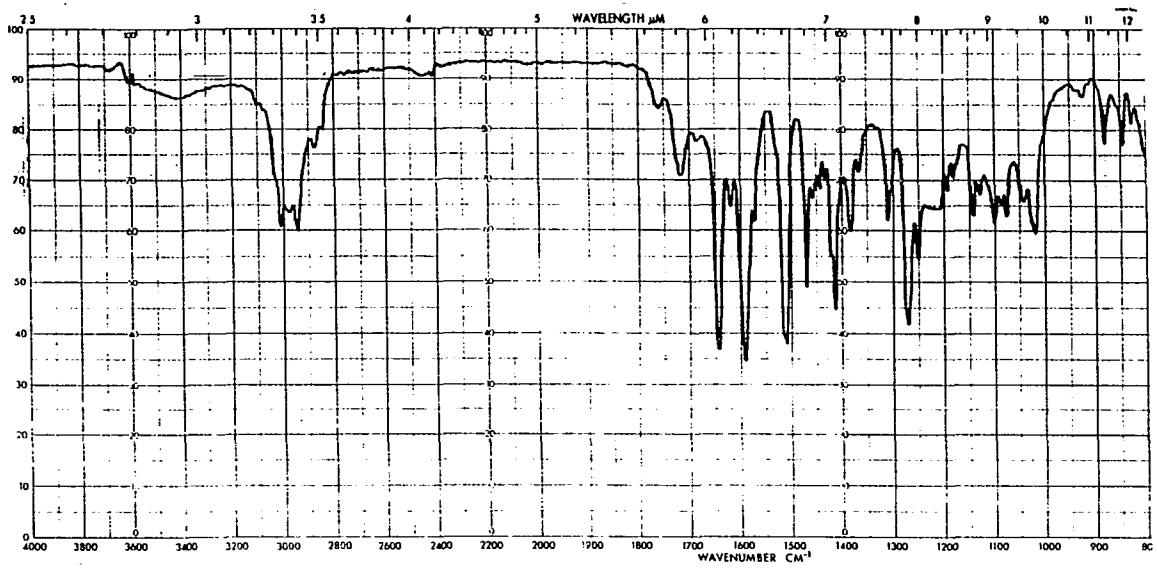
The N-ethyl oxopyrone (70 mg) was dissolved in 85 ml of glacial acetic acid. 16 g of activated zinc powder was added the mixture refluxed for 20 hours. The solution was filtered warm and diluted with ether. This solution was washed with 5% sodium hydroxide solution then with water and finally dried over $MgSO_4$. The dry solution was concentrated to 7 ml and allowed to stand in a refrigerator. After a few days, when no crystals had appeared the solution was made basic with 33% NaOH and extracted with chloroform. The solvent was removed to give 20 mg (29%) of an oil.

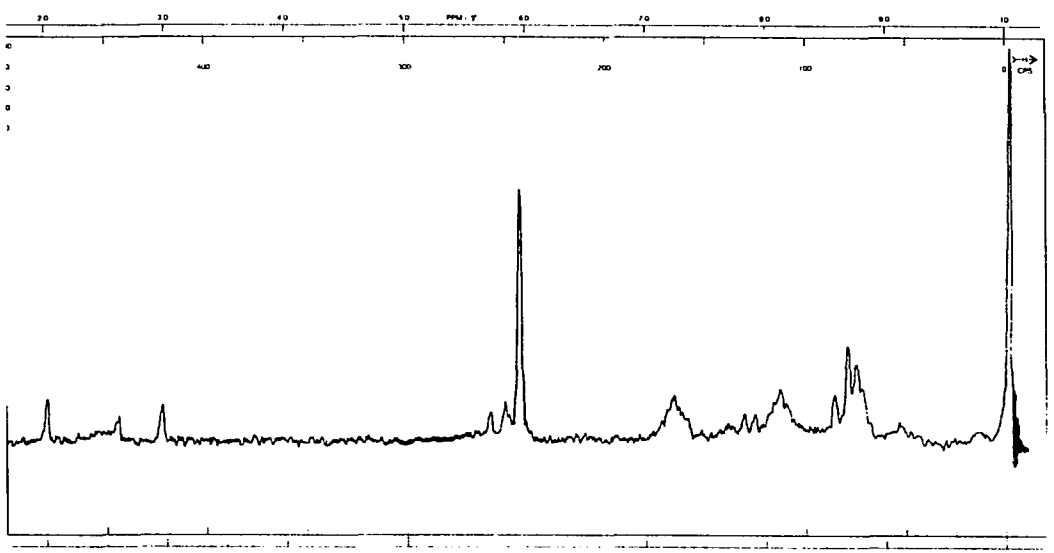
IR Figure 9 NMR Figure 9

1,2,3,4,5-Pentahydro-8,9-dimethoxyphenanthridone (40, R = H)

The dimethoxy compound from the acid hydrolysis of dimethoxy dimethyl acetal (38) (100 mg) was dissolved in 200 mg of glacial acetic acid. 20 g of zinc powder was added and the mixture refluxed for 24 hours. The hot solution was filtered and diluted with ether to form a white precipitate ($Zn(OAc)_2$) which was filtered. The filtrate was washed

Figure 9. IR and NMR spectra of N-ethyl-1,2,3,4-tetrahydro-8,9-dimethoxy-phenanthridone (40, R = ethyl)


WAVELENGTH μM
WAVENUMBER CM⁻¹



with 5% NaOH then with water and the organic layer dried over $MgSO_4$ and rotovaped until a precipitate appeared. This was collected by centrifugation and dried under vacuum to give a 20% yield of compound 40, R = H (dimethoxy) mp 274-279°C.

M.S. ($C_{15}H_{17}NO_3$) calculated 259.12084

found 259.11985

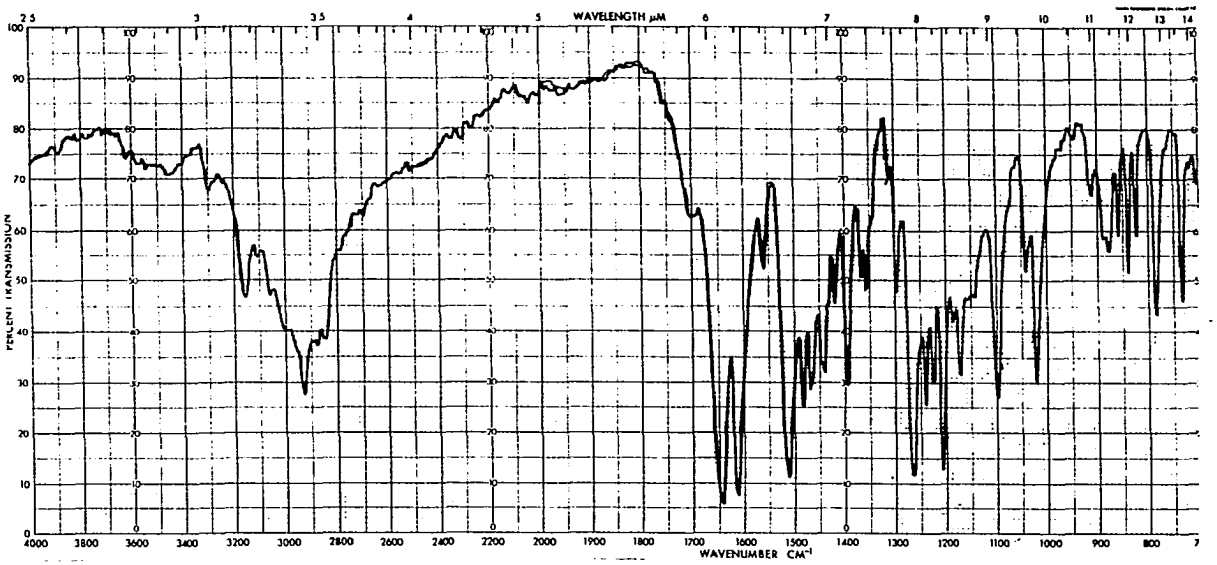
IR Figure 10 NMR Figure 10

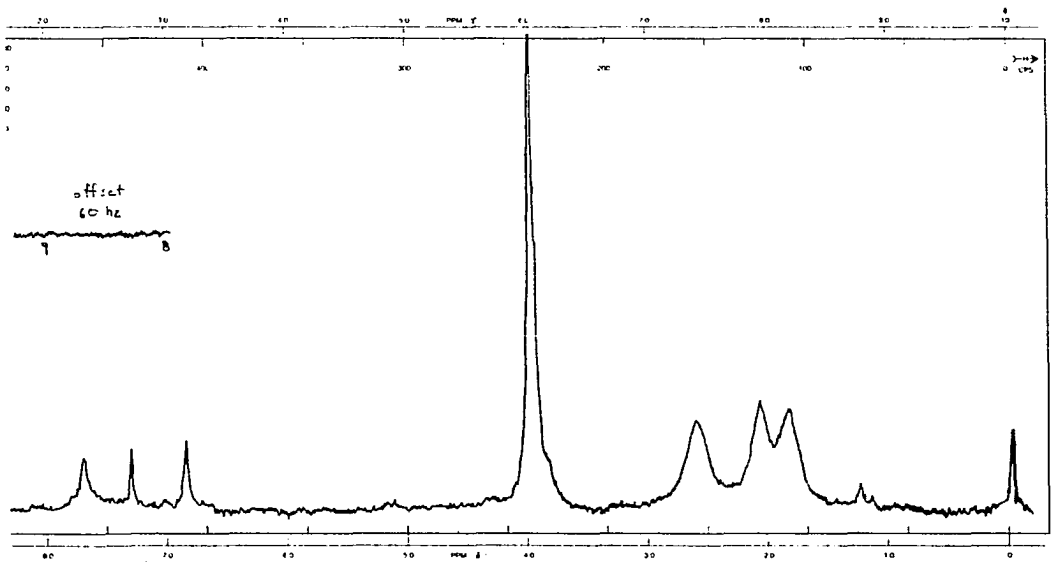
UV Figure 7

N-Ethyl-1-hydroxy-1,2,3,4-tetrahydro-8,9-methylenedioxy phenanthridine (41)

With lithium aluminum hydride The oxolactam (18, R = ethyl) (500 mg) was placed in the extraction thimble of a Soxhlet extraction apparatus and continuously extracted into 200 ml of dry ether containing one gram of lithium aluminum hydride. After two days, the excess hydride was destroyed with wet ether followed by two ml of 5% NaOH solution. This emulsion was filtered through Celite. The filtrate was dried and the solvent removed in vacuo to give 101 mg of material. Boiling the filter cake in chloroform and refiltering provided an additional 344 mg of material. Total yield 445 mg (98%). The compound was dissolved in benzene from which a white crystalline solid precipitated, yield 315 mg (42%), mp 174-8°C.

Figure 10. IR and NMR spectra of 1,2,3,4,5-pentahydro-8,9-dimethoxy-phenanthridone (40, R = H)


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION


offset
60 hz

With sodium borohydride The oxolactam (50 mg) was dissolved in 25 ml of absolute ethanol. A large excess of sodium borohydride was added portion-wise with gentle heating. The solution was allowed to cool for one hour then acidified first with boric acid and then with 25% HCl. The solution was diluted with ice water and suction filtered. The white powder was collected and proved to be identical to the above $LiAlH_4$ reaction product by TLC (100% ethyl acetate on silica gel) and IR, yield 31 mg (60%).

M.S. ($C_{16}H_{17}NO_4$) calculated 287.11576

measured 287.11533

fragmentation; (m - H_2O), (m - H_2O + CH_2=CH_2)

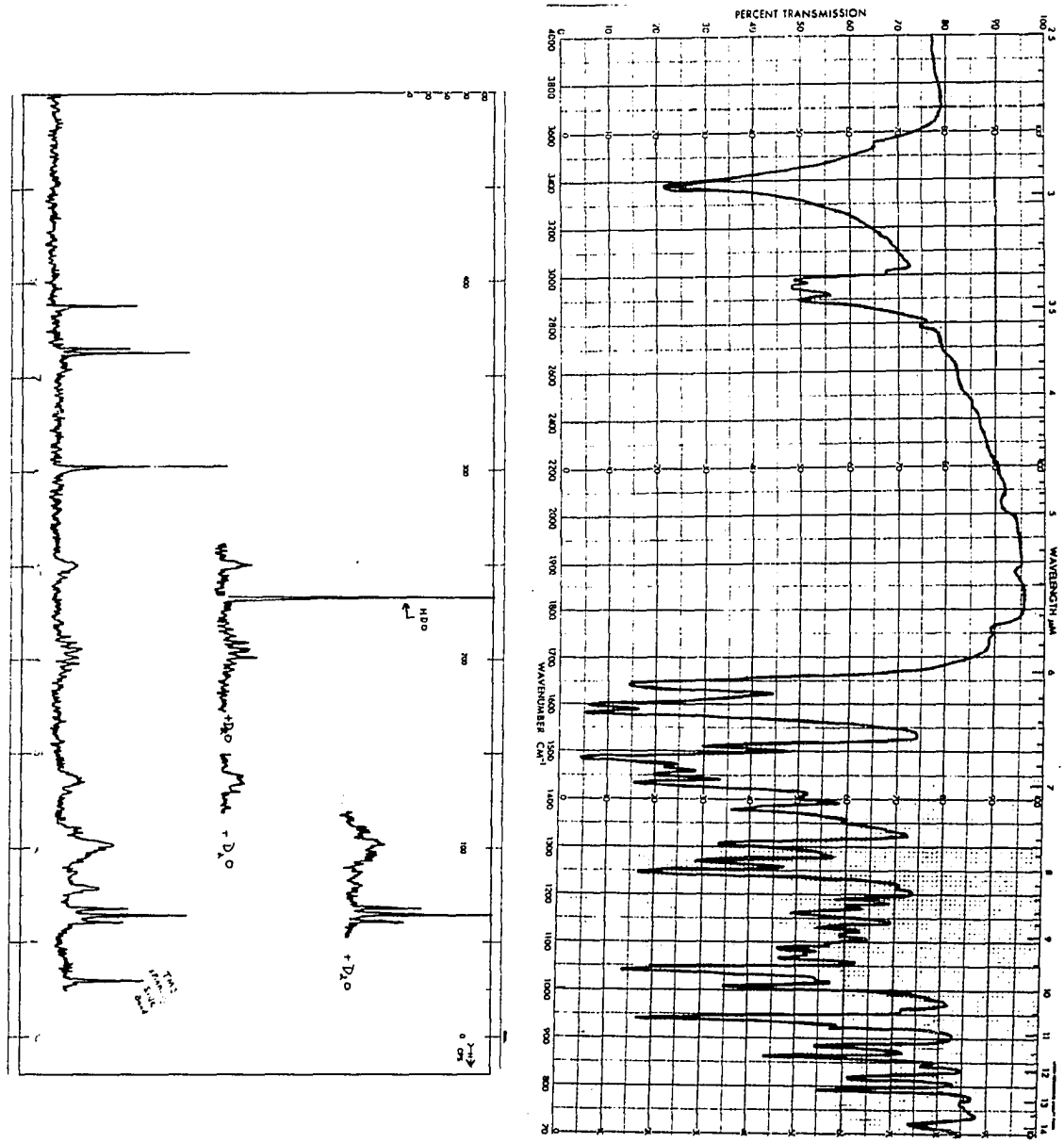
IR Figure 11 NMR Figure 11

Oxidation of 1-hydroxy compound (41)

With manganese dioxide 43 mg of compound 41 was dissolved in 30 ml of chloroform with 150 mg of activated manganese dioxide. After stirring 24 hours TLC showed no reaction and the reactant was recovered unchanged as observed by infrared spectroscopy.

With pyridinium chlorochromate 29 mg of compound 41 in 30 ml of methylene chloride was added to 32.3 mg (1.5 equiv) of pyridinium chlorochromate in 30 ml of methylene chloride and stirred overnight. Ethyl ether was added to make 100 ml then the mixture filtered by suction through a

Figure 11. IR and NMR spectra of N-ethyl-1-hydroxy-1,2,3,4-tetrahydro-8,9-methylenedioxyphenanthridone (41)


PERCENT TRANSMISSION
WAVELENGTH μM
WAVENUMBER CM⁻¹
HDO
+D₂O
+D₂O

pad of Florisil. The filtrate was evaporated to dryness and the residue recrystallized from methanol with the help of a seed crystal. The mp and infrared spectrum of the product was identical to the N-ethyl oxolactam 18 (R = ethyl).

Vigorous lithium aluminum hydride reductions of oxolactams

Compound 18, (R = H) Reduction could not be accomplished due to the insolubility of the reactant in ether solvents.

Compound 18, (R = ethyl) 75 mg of N-ethyl oxolactam was extracted in a Soxhlet apparatus into 100 ml of dry tetrahydrofuran containing 300 mg of lithium aluminum hydride. After refluxing for 20 hours the excess hydride was destroyed with wet tetrahydrofuran, 3 ml of 5% NaOH and 2 ml of water. The slurry was filtered through Celite. The filter cake was boiled in fresh THF and refiltered and the filtrates combined, dried and evaporated. The resulting oil was suspended in benzene and washed with water and the organic layer, containing 120 mg of material, was chromatographed on 5 g of alumina. The benzene elutant gave 27 mg of a compound which gave a negative siligotungstic acid test and this was discarded. Eluting with chloroform gave 41 mg (61%) of a compound giving a positive silicotungstic acid test. This compound was shown by infrared and nuclear magnetic resonance spectra to be compound 41 (R = ethyl).

IR Figure 12 NMR Figure 12

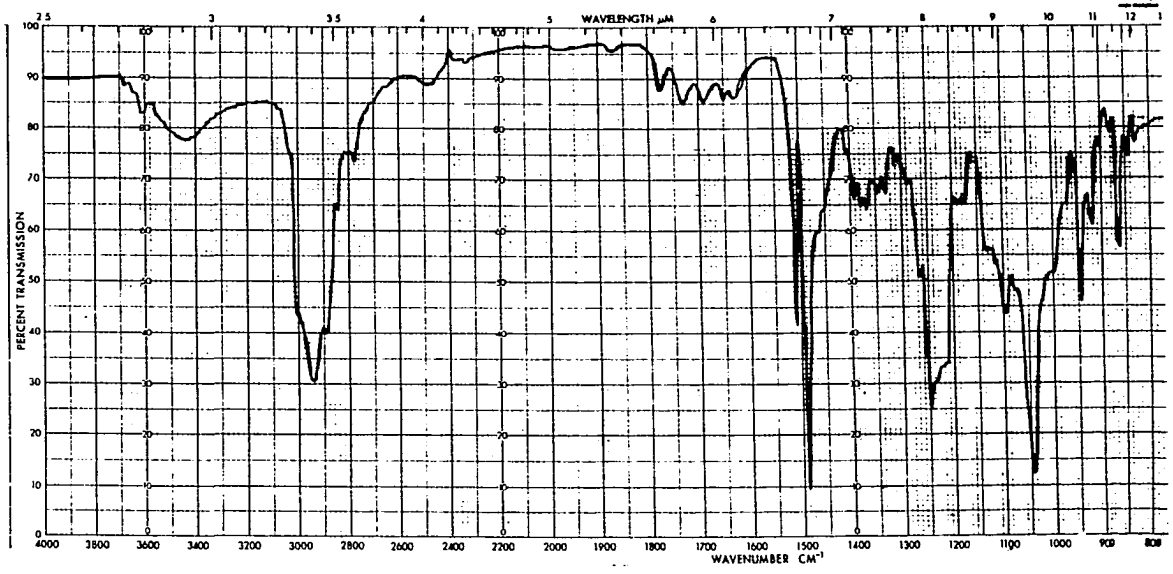
Compound 18, (R = CH_2CH_2OH) 300 mg of the ethanolamine adduct was reduced as above. Thin layer chromatography showed a complex mixture had been formed and column chromatography provided a large number of small fractions all giving positive silicotungstic acid tests. The reduction of this compound was deemed to be unuseful from a synthetic standpoint and was not repeated.

Compound 38 The dimethoxy dimethyl acetal (250 mg) was added to 400 mg of lithium aluminum hydride in 50 ml of dry diethyl ether. After refluxing for 24 hours, the excess hydride was destroyed with wet ether followed by 5 ml of 5% NaOH. The mixture was filtered through Celite and the filtrate dried and evaporated to dryness to yield 183 mg (80%) of an aminoacetal. The dimethyl acetal was intact as shown by NMR and the compound gave a positive silicotungstic acid test.

IR Figure 13 NMR Figure 13

The entire yield of acetal (183 mg) was dissolved in 10 ml of 10% HCl and heated on a steam bath for 15 min. This solution was washed with chloroform and basified to pH 8 with sodium bicarbonate. The basic solution was extracted with chloroform and the organic layer dried and evaporated to a red oil weighing 135 mg (86%).

Figure 12. IR and NMR spectra of N-ethyl-2,3,4,4a,6-pentahydro-8,9-methylene-dioxyphenanthridine (42, R = ethyl)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

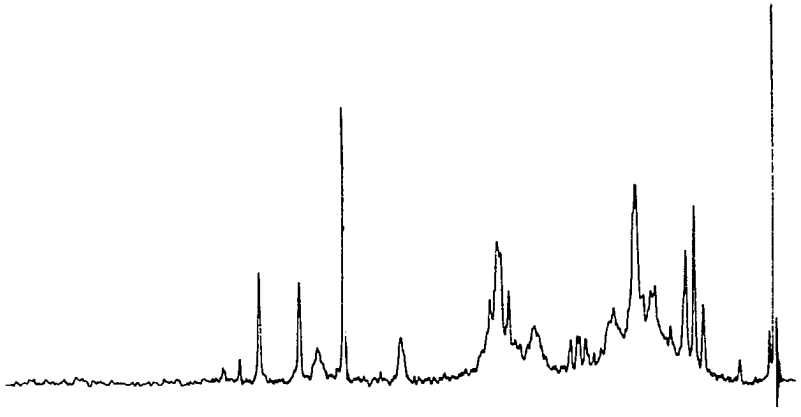
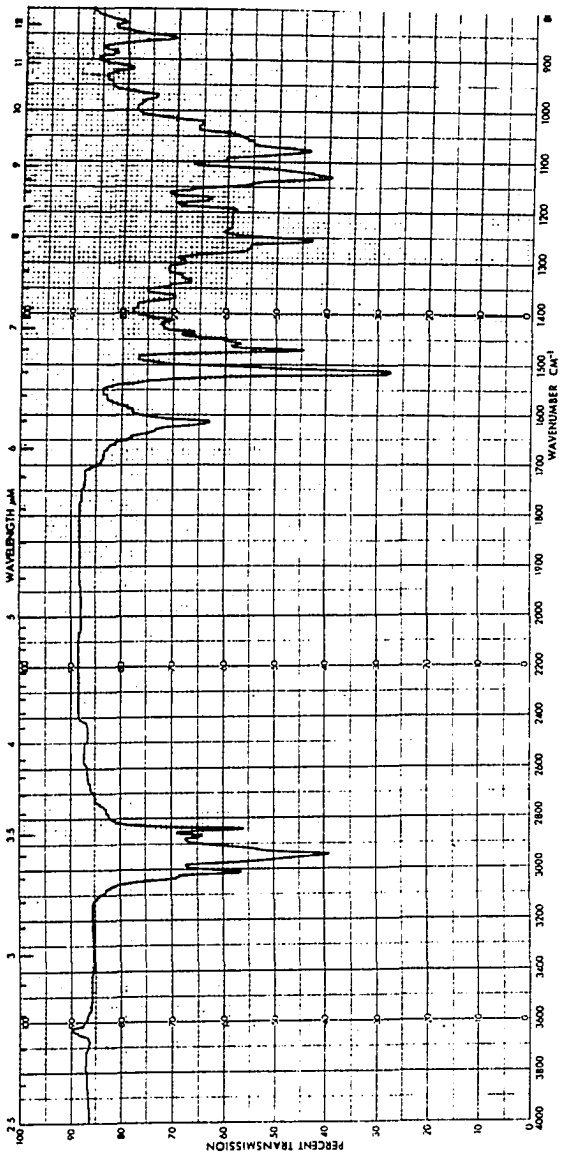
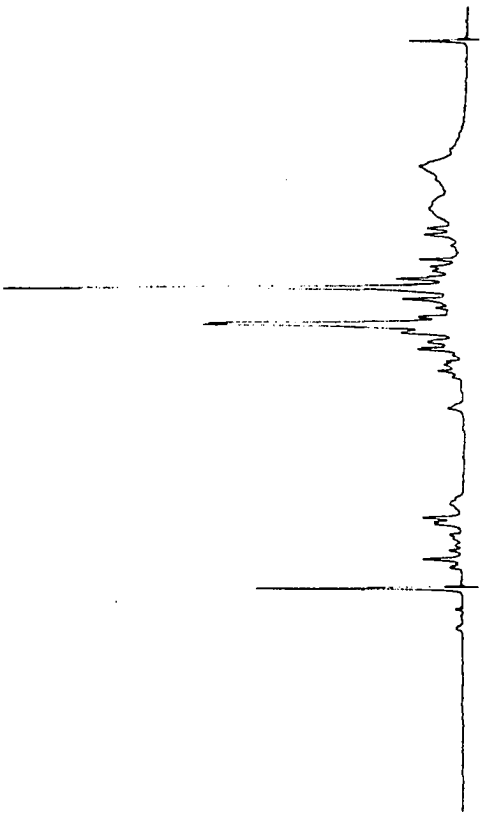


Figure 13. IR and NMR spectra of N-(2,2-dimethoxyethyl)-2,3,4,4a,6-pentahydro-8,9-dimethoxyphenanthridine (42, R = $CH_2CH(OCH_3)_2$)


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION



The oil was chromatographed on 20 g of silica gel and eluted, with 90/10; chloroform/ethyl acetate, to give 54 mg of an aldehyde which gave a positive silicotungstic acid test.

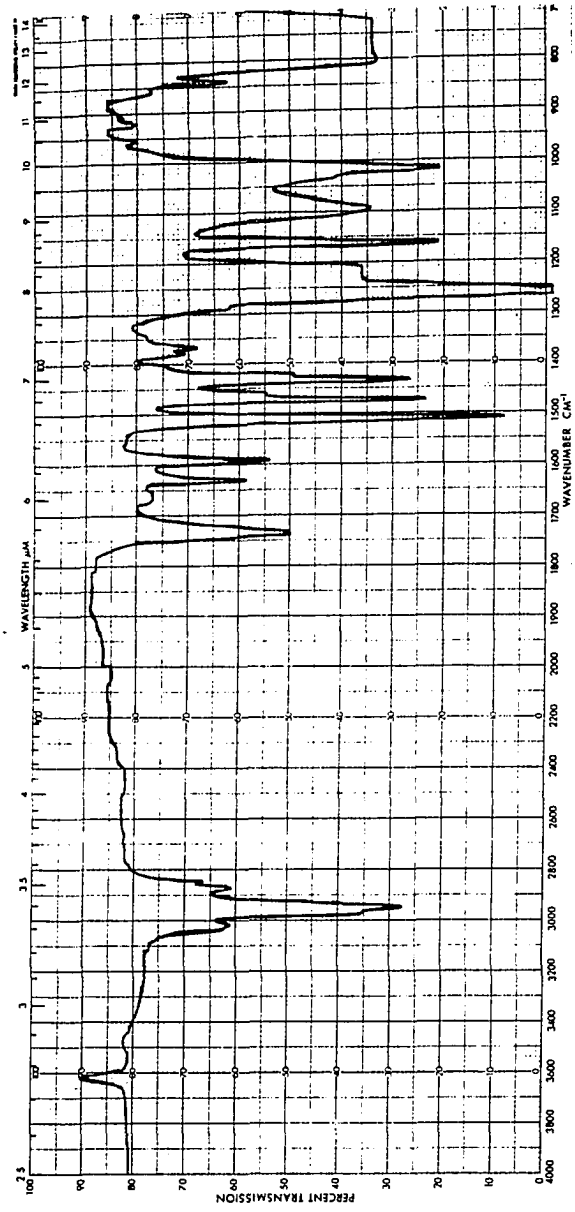
IR Figure 14 NMR Figure 14

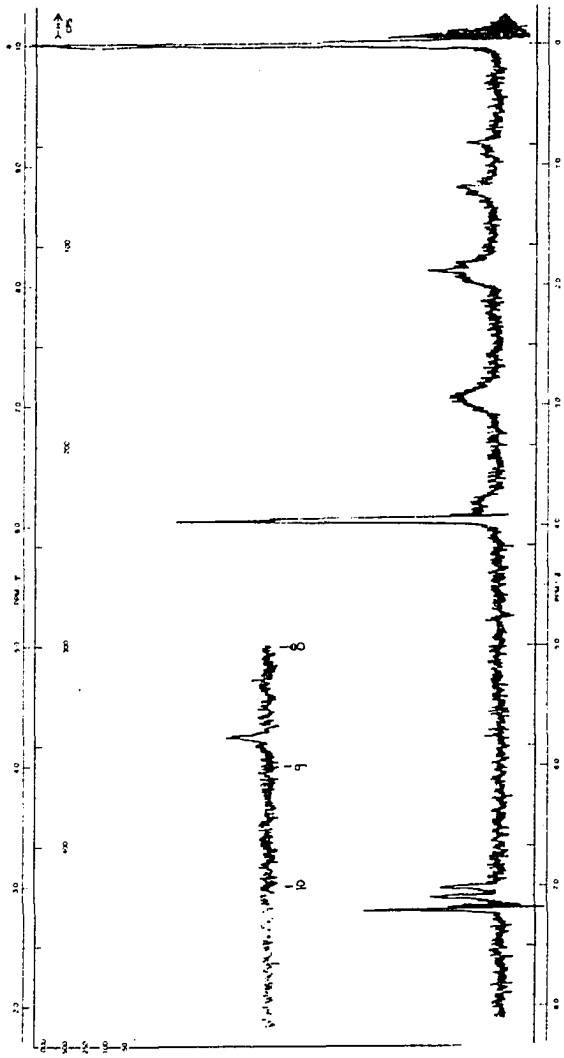
Attempted hydroboration of 41 (R = $CH_2CH(OCH_3)_2$)

The lithium aluminum hydride reduction product of compound 38 (700 mg) was dissolved in 10 ml of dry tetrahydrofuran. To this solution was added 23 mg of sodium borohydride followed by 1 ml of borontrifloride-etherate in 5 ml of tetrahydrofuran. The addition of the Lewis acid took 10 min. The reaction mixture turned from colorless to yellow and finally to orange as it was stirred for 25 min. Water (1.5 ml) was added slowly, turning the solution back to yellow. Hydrogen was evolved and the temperature rose to 30°. Sodium hydroxide (3 N) (1.5 ml) was added in one portion followed by dropwise addition of 1.5 ml of hydrogen peroxide (30%). When addition was complete the temperature was raised to 50° and maintained for 30 min after which the heat was removed and 25 mg of sodium chloride was added. The mixture was poured into a separatory funnel and washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness to yield 832 mg of yellow oil (theoretical 740 mg).

A portion (155 mg) of the hydroboration-oxidation product was dissolved in 5 ml of 10% HCl and washed with hexane.

Figure 14. IR and NMR spectra of aldehyde of compound 42 (R = $CH_2CH(OCH_3)_2$)


PERCENT TRANSMISSION
WAVELENGTH μM
WAVENUMBER CM⁻¹



The aqueous layer was basified with ammonium hydroxide and extracted with chloroform. The organic layers were combined, dried, and evaporated to give 120 mg of a green oil which gave a positive silicotungstic acid test. Unfortunately, both the infrared and nuclear magnetic resonance spectra were identical with the starting acetal 37, indicating that hydroboration had not taken place.

PART II: MODIFICATIONS OF CRININE ALKALOIDS FOR THE SYNTHESIS OF PRETAZETTINE AND PRECRIWELLINE

INTRODUCTION

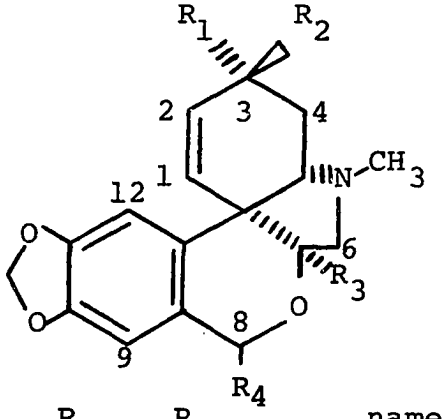
The Amaryllidaceae alkaloids pretazettine and precriwelline have been found to possess therapeutic activity against a leukemia virus. In an effort to determine the pharmacologically active portion of these molecules a number of analogs and derivatives were tested. The results of these tests are still incomplete but some structure-activity relationships have become apparent. More work to fully elucidate the pharmacophoric moiety is needed. This dissertation adds to the present knowledge of the synthesis of pretazettine and precriwelline analogs and derivatives by modification of other Amaryllidaceae alkaloids. This was accomplished mainly through the use of cyanogen bromide cleavage of alkaloids followed by benzylic oxidation.

HISTORICAL

Modifications of Amaryllidaceae Alkaloids

Pharmacology of pretazettine and precriwelline

Pretazettine (1a) has been shown by Furusawa et al. (53) to be an extremely effective therapeutic agent against advanced Rauscher Leukemia in mice. Subsequently, numerous other Amaryllidaceae alkaloids and their derivatives have been screened to determine their effectiveness against the virus (54, 55).



44

	R_1	R_2	R_3	R_4	name
a)	H	OCH_3	H	OH	pretazettine
b)	OCH_3	H	H	OH	precriwelline
c)	H	OCH_3	OH	H	tazettine
d)	OCH_3	H	OH	H	criwelline
e)	H	OCH_3	H	H	deoxytazettine
f)	OCH_3	H	H	OCH_3	O-methylprecriwelline
g)	H	OCH_3	H	OCH_2CH_3	O-ethylpretazettine

Pretazettine (44a) has been shown by Furusawa and coworkers (56) and by Spanish workers (57, 58) to block cellular protein synthesis. The Spanish group reported that

pretazettine, narciclasine and haemanthamine (46a) all bind to the 60s subunit of eucaryotic ribosomes, interfering with peptidyl transferase binding. The alkaloid lycorine, however, had no such inhibitory effect (59, 60).

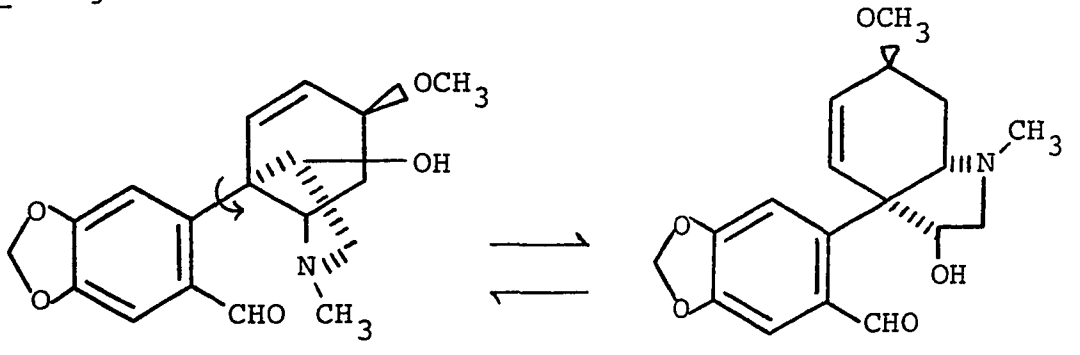
Furusawa tested both the cytotoxicity of the alkaloids against the virus in culture and the ability of the drugs to prolong the life of a mouse infected with the virus.

Precriwelline (44b) has exactly the same activity as pretazettine, indicating that perhaps the C-ring is not part of the pharmacophoric moiety of the molecule. If the methoxy group on the C-ring is removed and the double bond saturated, a compound with virtually no activity is produced. These findings suggest that although the stereochemistry of the C-3 methoxyl is unimportant, its presence in the molecule along with the rigidity imparted by the double bond is essential. If the double bond is moved to the C-2, C-3 position and the methoxyl removed, activity is greatly enhanced over the compound having an unfunctionalized C-ring. Thus, (dl)-demethoxyisopretazettine has one-twentieth of the activity of the parent, optically active, alkaloid and is a hundred times more potent than (dl)-demethoxydihydropretazettine.

The hemiacetal moiety seems to be essential for therapeutic action since there is a four hundred-fold loss of activity upon O-methylation of precriwelline to 44f.

Lengthening of the acetal side chain, however, seems to restore some activity. Accordingly, O-ethylpretazettine (44g) suffers only a twenty-fold activity loss.

Laboratory and plant synthesis of pretazettine and precriwelline stem from rearrangements of the crinine-type alkaloids. It can be seen that, once the nitrogen has been methylated, the hemiaminal is in equilibrium with the free aldehyde which in turn is capable of rotation about the 10a-10b bond and acetal formation with the hydroxyl at C-11. For example, haemanthidine (46b) can be N-methylated and will then open up to the free aldehyde (45). Free rotation is now possible as indicated by the curved arrow and conformer 45b is generated.

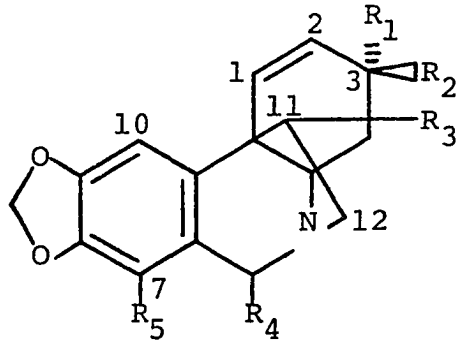


45a 45b

Intermediate (45b) can then form the hemiacetal and produce pretazettine (44a). It is now easy to see why the methiodide of 6-hydroxycrinamine (46b) is every bit as active as its rearranged form, precriwelline. Some of the alkaloids tested were in the form of their methiodides and the rest

were tested as their hydrochlorides. This was done to increase their water solubility.

Crimanine (46c) and haemanthamine (46a) are equally active but are only one fourth as potent as their 6-hydroxy analogs. This is probably due to the fact that an additional step, benzylic oxidation, is necessary to transform these alkaloids into active compounds.

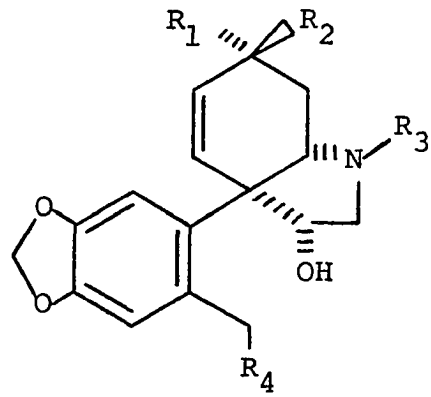


46

	R_1	R_2	R_3	R_4	R_5	
a)	H	OCH_3	OH	H	H	haemanthamine
b)	H	OCH_3	OH	OH	H	haemanthidine
c)	OCH_3	H	OH	H	H	crinamine
d)	OCH_3	H	OH	OH	H	6-hydroxycrinamine
e)	OH	H	H	H	H	crinine
f)	OH	H	H	H	OCH_3	powelline
g)	OCH_3	H	H	H	H	buphanisine
h)	OCH_3	H	H	H	OCH_3	buphanidrine
i)	OCH_3	H	H	OH	OCH_3	6-hydroxybuphanidrine
j)	-O-	H	-O-	OH	H	apohaemanthidine

The abundant alkaloid tazettine (44c), now known to be an artifact caused by base induced rearrangement of pretazettine (44), has only one four-hundredth of the activity of

its precursor. Chemical modifications of tazettine have proved unrewarding. Tazettadiol (47a), the least active of all the compounds yet reported, is formed by lithium aluminum hydride reduction of tazettine. Selective benzylic oxidation of tazettadiol should produce a compound which is the epimer of pretazettine at C-6a. Manganese dioxide oxidation products as well as chromium trioxide oxidation products of tazettadiol were all inactive. Since the structures of these oxidation products were not determined, it is hard to draw any conclusions regarding the possibility of activity of the epipretazettine.



47

	R_1	R_2	R_3	R_4	
a)	H	OCH_3	CH_3	OH	tazettadiol
b)	OCH_3	H	CN	Br	crinamine cyanobromide

Ring closure of tazettadiol under acidic conditions gave the cyclic ether deoxytazettine (44e) which was no more active than tazettadiol itself.

In view of these facts it seems unusual that crinamine cyanobromide (47b), made by von Braun degradation of

crinamine, is as active as it is. Although 47b is similar structurally to 47a, which is for all practical purposes inactive, it has more than forty times the activity of tazettadiol albeit one hundredth the strength of pretazettine.

The necessity of the 11-hydroxy group for activity was explored by testing two compounds. In the methiodide of apoheamanthidine (46j) the 11-hydroxy group is tied up in a cyclic ether and in the methiodide of 6-hydroxybuphanidrine (46i) the 11-hydroxy group is absent. Loss of activity of these two compounds relative to pretazettine is explained by their inability to form hemiacetals after the 45a-45b-type equilibrium has been established. Additionally, 46i has a bulky methoxy group in the 7-position which may interfere with the pharmacophoric region. Table 3 is a listing of the above data. Entries are listed in order of their decreasing activity towards Rauscher Leukemia in mice.

To summarize the current findings, pretazettine or precriwelline or molecules capable of transformation into them in vivo are most active. It seems that the C-ring is not heavily involved in the pharmacophoric center but that the double bond in the C-ring is necessary. The 11-hydroxy group is required in crinine-type alkaloids so that hemiacetal formation is possible. A free and unhindered hemiacetal is

Table 3. Minimum cytotoxic dose (MCD) of some amaryllidaceae alkaloids against Rauscher Leukemia in mice

Compound	MCD (μg/ml)	Structure
narciclasine	.005	24
pretazettine	.05	44a
precriwelline	.05	44b
6-hydroxycrinamine methiodide	.05	46d
crinamine	.2	46c
haemanthamine	.2	46a
(dl)-demethoxyisopretazettine	1	---
O-ethylpretazettine	1	44g
crinamine cyanobromide	5	47a
O-methylprecriwelline	20	44f
tazettine	20	44c
apohaemanthidine methiodide	25	46j
6-hydroxybuphanidrine methiodide	100	46i
(dl)-demethoxydihydropretazettine	100	---
tazettadiol MnO_2 products	100	---
tazettadiol CrO_3 products	100	---
tazettadiol	200	47b
deoxytazettine	200	44e

most active although a long aliphatic chain from O-alkylation will also work, possibly due to increased cell membrane permeability.

Although the possibilities for modification of the pretazettine structure are far from exhausted, it is clear that pretazettine and precriwelline are the most effective

therapeutic agents available against Rauscher Leukemia virus. While it would be desirable to continue research on the determination of the pharmocophoric moiety, it also seemed worthwhile to examine the chemical conversion of other Amaryllidaceae alkaloids, especially those of the crinine-type, to pretazettine. This goal is most easily accomplished by benzylic oxidation of haemanthamine and crinamine to their 6-hydroxy derivatives. These may then be N-methylated and rearranged to pretazettine and precriwelline, respectively.

von Braun reaction of some Amaryllidaceae alkaloids

Benzylic oxidation in the laboratory is sometimes difficult. Direct vigorous oxidation of a suitably protected alkaloid with potassium permanganate often gives poor yields of a lactam. These are then difficult to reduce only partially to the oxidation state of a hemiaminal. A more rewarding procedure has been a stepwise one. Cyanogen bromide cleavage of the alkaloid gives a N-cyano group and, under the right conditions, a benzyl bromide. The benzyl bromide may then be oxidized by a number of well-known reagents to an aldehyde, the desired oxidation state.

The von Braun reaction (61), cleavage of tertiary amines with cyanogen bromide, is a common alkaloid degradative procedure. An exhaustive review of this reaction is not possible in this dissertation but an overview of cyanogen bromide chemistry as applied to Amaryllidaceae

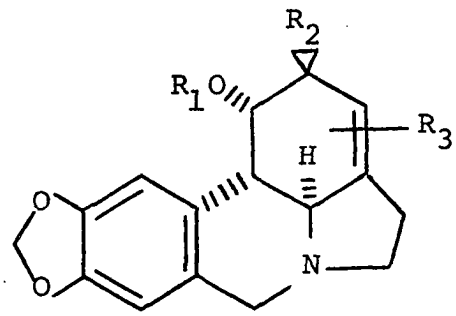
alkaloids is certainly in order. A complete list of Amaryllidaceae derived compounds which have been subjected to the von Braun reaction is presented in Table 4.

Table 4. Reaction of cyanogen bromide with Amaryllidaceae alkaloids

Substrate	Structure	Product	Reference
lycorine	48c	no rxn	61
dihydrolycorine	48d	49a	61
O,O-diacetyllycorine	48e	51	62
O,O-diacetyllycorine	48e	51 + 52	61
O,O-diacetyllycorine	48e	51 + 52	63
α-dihydrocaranine	48b	---	64
clivonine	53a	54a	65
acetylclivonine	53b	54b	65
deoxyclivonine	---	---	65
crinamine	46c	47b	54

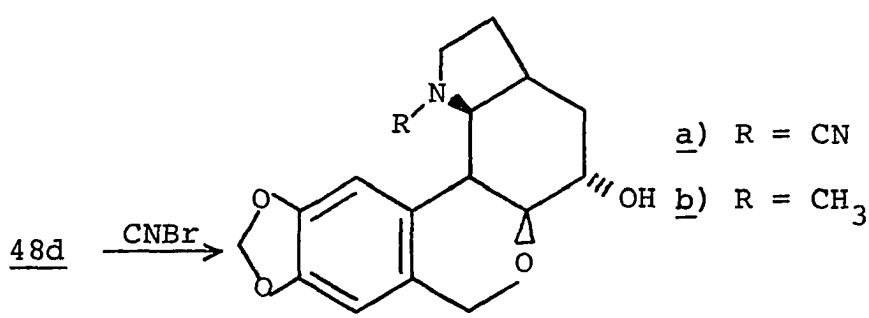
Cyanogen bromide has not been used much as a tool for the elucidation of gross structure but rather as a method of determining the stereochemistry of alkaloids. Lycorine (48c), whose structure has been known for some time, was the first member of the Amaryllidaceae alkaloids to be reacted with cyanogen bromide.

Lycorine itself is unreactive towards cyanogen bromide due to its low solubility in organic solvents (62). Dihydrolycorine (48d), however, reacts to give a single product (49a



48

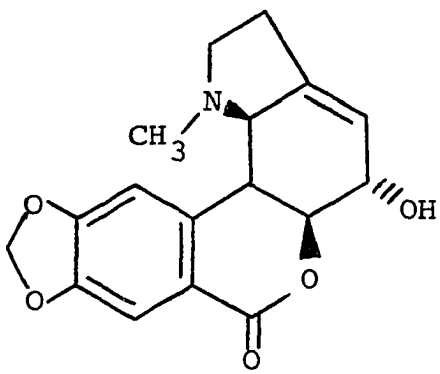
	R_1	R_2	R_3	
a)	H	H	---	caranine
b)	H	H	αH_2	dihydrocaranine
c)	H	OH	---	lycorine
d)	H	OH	αH_2	dihydrolycorine
e)	Ac	OAc	---	O,O-diacetyllycorine



49

Compound 49a was converted to the N-methyl compound 49b by lithium aluminum hydride followed by Eschweiler-Clarke methylation. This compound was also made from hippeastrine (50). Since 49b was made from both a lycorine-type alkaloid

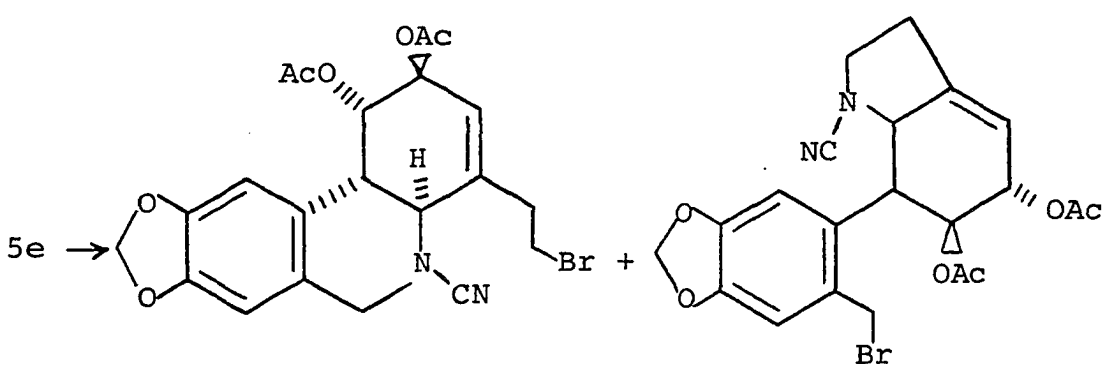
and a lycorenine-type alkaloid, it was reasoned that the absolute configurations of these two types of alkaloids were identical.



50

→ 49b ← 48d

O,O-diacetyllycorine has given two cleavage products, although a preliminary study by Kondo and Katsura (63) reported that only one compound was obtained. Kotera and coworkers (62) obtained both the product of Kondo and Katsura (51) and a product resulting from benzylic cleavage (52).



51 52

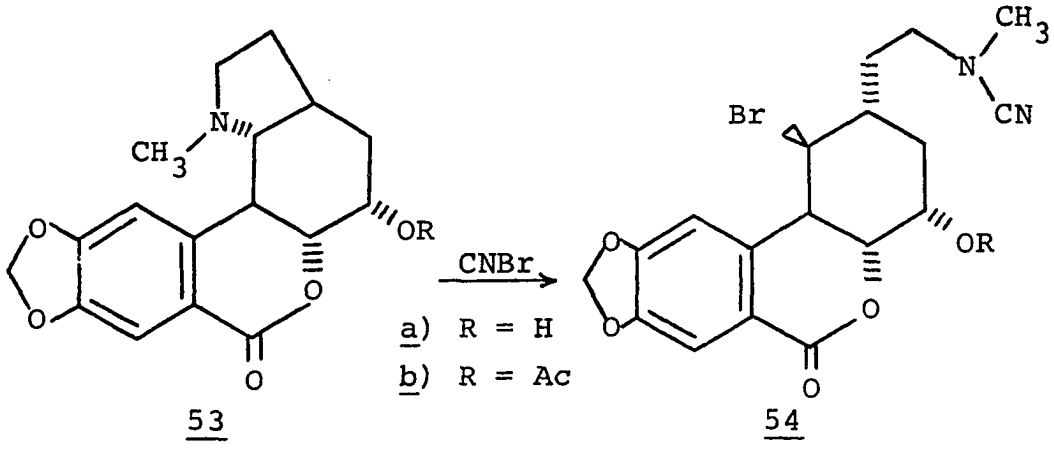
Compound 52 was converted in five steps to hippeastrine (50) giving additional support to the hypothesis that the lycorine and lycorenine ring systems are interrelated.

The ratio of products 51 and 52 was found to be 2:1 by Kotera and coworkers using benzene as a solvent. Christenson (64), however, found that this ratio could be reversed if chloroform were used instead. Christenson went on to oxidize the benzylic bromide in 52 to the corresponding aldehyde which he then masked as its dimethyl acetal. Lithium aluminum hydride removed the N-cyano and acetate groups and allowed the aldehyde group, once released, to react with either the secondary amine or the alcohol group at C-1. The results were ambiguous and the existence of the hemiacetal or the hemiaminal thus formed was dependent on the conditions used to detect them.

In a manner analogous to that described for dihydrolycorine, α-dihydrocaranine (48b) was converted into α-deoxydihydrolycorenine (65).

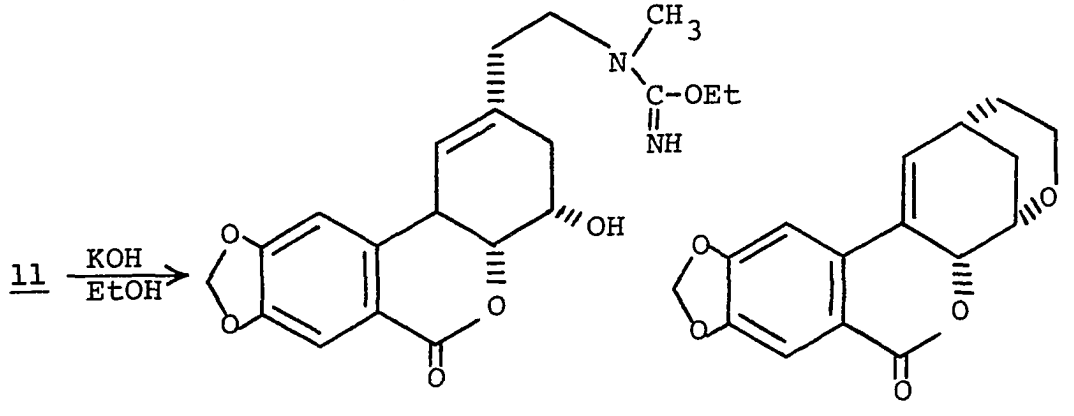
Finally, in a series of reactions calculated to reveal the relative stereochemistry of a single alkaloid, Jeffs and coworkers (66) treated clivonine (53a) with cyanogen bromide to give a single product (54a).

Jeffs' plan was to hydrolyze the N-cyano group, exhaustively methylate the amine and displace it with the free hydroxyl to form 55. The existence of this cyclic



53 54

ether would establish the fact that the hydroxyl group is cis to the pyrrolidine ring. Compound 56 could not be made due to the stability of the intermediate imino-ether (55) formed by basic hydrolysis of 54.



55 56

Deoxyclivonine gave results completely analogous to clivonine in the von Braun reaction.

RESULTS AND DISCUSSION

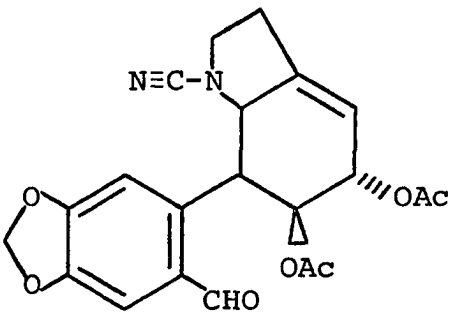
Modification of Lycorine

One of the purposes of this dissertation was to repeat and verify the work of Christenson (64) on the chemical conversion of lycorine to 7-hydroxylycorine and/or a lycoreneine-type alkaloid.

Lycorine was first acetylated. This was done for several reasons, not the least of which was solubility enhancement. Also, an unprotected hydroxyl at C-1 would react with the benzyl bromide to be formed in the next step to form a cyclic ether. The diacetate was then subjected to the von Braun reaction to give a mixture of products as originally reported by Christenson. The infrared spectrum was clean and sharp and gave no indication that a mixture might be present. The integration of the NMR peaks, however, indicated at least a 3:1 predominance of the benzyl bromide.

Without purification the cyanobromides were oxidized with dimethylsulfoxide and sodium bicarbonate at 120°C. Under these conditions only the benzyl bromide could be expected to react to give an aldehyde while the second isomer would be inert. Again, Christenson's work was confirmed as the aldehyde was recovered in pure form after purification by column chromatography on silica gel. The unreacted 1° bromide was eluted first as a red oil using 3:1 chloroform: benzene. The aldehyde was eluted with 100% chloroform and

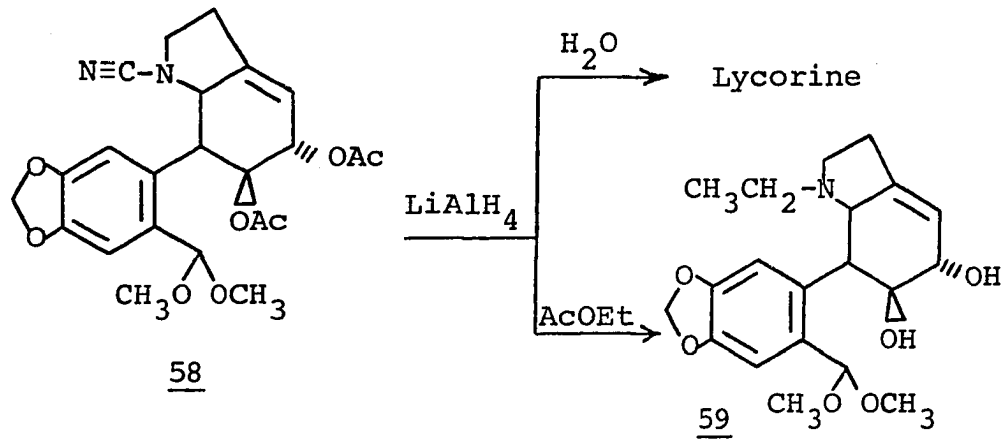
recrystallized from ethyl acetate. Its structure (57) was confirmed by infrared, nuclear magnetic and ultraviolet spectra and a satisfactory elemental analysis.



57

The dimethyl acetal of 57 was made with trimethylorthoformate in acidic methanol. Refluxing for 3 hours was sufficient to transform all of the aldehyde to its acetal (58). The acetal could not be crystallized and was unstable having a shelf life of less than 48 hours. For this reason the acetal was used immediately after it was formed.

Lithium aluminum hydride reduction of the acetal in tetrahydrofuran gave surprising results. If, after ten hours in refluxing tetrahydrofuran, the excess hydride was destroyed slowly with an aqueous solution of sodium potassium tartrate, a white crystalline substance was isolated in 15% yield. The compound was identified by its melting point and infrared spectrum as lycorine. If, on the other hand, the excess hydride was destroyed by slow addition of ethyl acetate the N-ethyl diol 16 was obtained in 50% yield.

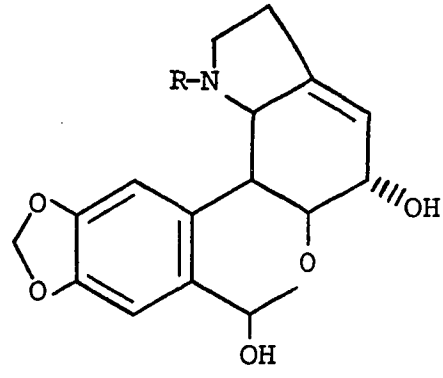


58 59

The production of lycorine can be explained in the following manner. Acetal (58) is reduced to the secondary aminodiol as would be expected. Slow addition of water causes the destruction of the acetal protecting group faster than the destruction of the large excess of hydride. The aldehyde thus formed reacts rapidly with the free secondary amine intramolecularly and the resulting hemiaminal is reduced to the amine, lycorine, by the remaining hydride.

In the case of the N-ethyl product, ethyl acetate reacts with the secondary amine to form an N-acetate and ethanol. This amide is quickly reduced by the remaining hydride (67).

The structure of 59 at first proved elusive. Acetylation gave a diacetate, which upon hydrolysis, produced an aromatic aldehyde. If the acetal (59) was first hydrolyzed then the hemiacetal (60, R = ethyl) was obtained.



60

Compound 60 (R = ethyl) was characterized as its methyl and ethyl acetals. Manganese dioxide oxidation of the hemiacetal provided a mixture of the lactone and the enone, as there are two possible sites of MnO_2 attack. Compound 60 (R = ethyl) was further characterized by a full compliment of spectroscopic methods including mass spectroscopy.

Christenson quenched his lithium aluminum hydride reactions quickly and thus did not observe these products.

In an attempt to arrive at a deacetylated aldehyde without the use of a hydride reducing agent the protected aldehyde (57) was treated with methanolic potassium carbonate. While this procedure did remove the acetate groups it failed to completely remove the cyano group. The hydrolysis gave not a secondary amine but an imino ether, 60 (R = CNH(OMe)).

Modification of Crinine-type Alkaloids

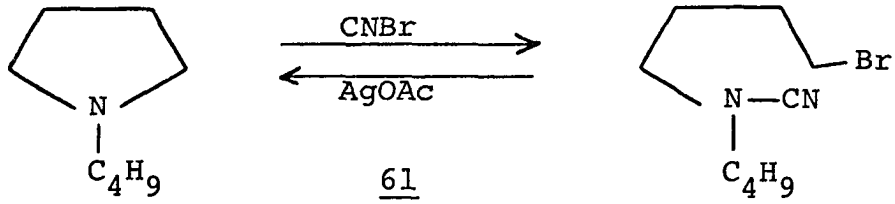
Crinine-type Amaryllidaceae alkaloids have never been subjected to the von Braun degradation. The reaction,

however, was found to occur in high yield to produce a single isomer in all of the cases that were tried.

Haemanthamine, powelline and acetylpowelline were all cleaved in mild fashion with cyanogen bromide in methylene chloride to yield exclusively the benzyl bromides. Powelline cyanobromide, when acetylated gave a product identical to the cyanogen bromide adduct of acetylpowelline.

The von Braun reaction could be reversed and the alkaloidal substrate recovered by subjecting the cyanobromide to silver acetate in acetic anhydride and acetic acid (68). The mechanism of this reverse von Braun reaction has not been proven but must consist of a silver assisted loss of bromide ion by backside attack of the benzylic carbon by the nitrogen atom. The resulting ammonium ion loses CN^+ to give the starting alkaloid. The eventual fate of the cyano group is unclear but analysis of the reaction mixture for cyanide ion gives a negative result.

The reverse von Braun reaction is not confined to alkaloids. The cyanobromide of 1-n-butylpyrrolidine affords the tertiary amine upon silver acetate treatment (61).



61

The above technique suggests a new synthesis of tertiary amines from secondary cyanoamines. The present method for

alkylating cyanoamines consists of hydrolysis of the cyano group to form a secondary amine followed by any of the standard amine alkylation methods. Treatment of the cyanoamine with silver acetate and the appropriate alkyl bromide would provide a tertiary amine free of quaternary amine salts in a single step.

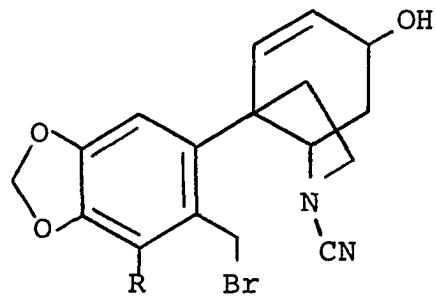
That the mechanism does indeed require a silver assisted abstraction of bromide ion is supported by the fact that the cyanoaldehyde (57) is inert towards silver acetate. Furthermore, the attempted oxidation of powelline cyanobromide with dimethylsulfoxide and silver acetate gave only powelline as a product.

Powelline cyanobromide was converted to powelline by another process without the use of a silver catalyst. When the cyanobromide was treated with lithium aluminum hydride in tetrahydrofuran the N-cyanogroup was removed but steric hinderance prevented hydrogenolysis of the benzylic bromide. Thus, when the reduction mixture was quenched, the secondary amine reacted intramolecularly with the benzyl bromide to regenerate powelline (46f).

The benzylic bromides produced by cyanogen bromide cleavage should be good substrates for oxidation to the corresponding aromatic aldehydes. Diacetyllycorine cyanobromide was oxidized to the aldehyde (57) with dimethylsulfoxide and sodium bicarbonate at 120°C. These conditions were also

employed in the attempted oxidation of the cyanobromides, of haemanthamine, and powelline. In addition, the cyanobromides of haemanthamine and powelline were subjected to the Sommelet reaction and powelline cyanobromide was treated with several other oxidizing systems including silver nitrate-dioxane-KOH-water, copper nitrate-water, and DMSO-silver acetate-triethylamine. No evidence of aldehyde was ever observed for any of the above experiments involving a crinine-type alkaloid.

In the case of powelline cyanobromide (62, R = OMe) attack at the benzylic carbon is effectively blocked by the two bulky ortho substituents, as was shown by its reaction with lithium aluminum hydride. Powelline cyanobromide also failed to react with sodium carbonate in acetone-water.



62

Crinine cyanobromide (62, R = H) and haemanthamine cyanobromide have only one ortho substituent as does the lycorine derivative. That the lycorine derivative reacts

with DMSO to give an aldehyde and the crinine derivatives do not must therefore be due to the atoms attached to the carbon that is alpha to the aromatic ring. The lycorine derived compound has an alpha hydrogen whereas the crinine-type compounds have a quaternary carbon in the alpha position. This situation can be likened to the steric difference between an isopropyl group and a tert-butyl group attached to the aromatic ring. Framework molecular models confirm this hypothesis as they show at least one conformation which allows unhindered attack in the lycorine case but no favorable conformations for the crinine series.

SUMMARY

The work of Christenson on the modification of lycorine was duplicated and verified but no further conclusions could be drawn.

Three members of the crinine family of alkaloids were cleaved by the von Braun reaction, thus expanding the present knowledge of this degradative technique in the Amaryllidaceae family of alkaloids. A means was found whereby the cyanobromides formed by the von Braun reaction could be returned to their precursors using silver acetate.

It was found that although diacetyllycorine cyanobromide was readily oxidized to the corresponding aromatic aldehyde, the analogous crinine-type cyanobromides were extremely reluctant to undergo oxidation. This was rationalized on the basis of differing steric environments at the reaction site.

EXPERIMENTAL

Instrumentation

Melting points were taken on a Köfler hot stage microscope with polarizing filter and are corrected. Infrared spectra were run on a Beckman Model IR 4250 spectrometer in chloroform solution or in a potassium bromide pellet. Ultraviolet-visible spectra were obtained on a Cary Model 14 spectrophotometer in 95% ethanol solution through quartz cuvettes. 50 MHz proton magnetic resonance spectra were run on either a Hitachi Perkin-Elmer Model R-20B, Varian Model A-60 or a Varian EM 360. 100 MHz spectra were obtained on a Varian Model HA-100. All chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were run on a A.E.I. MS 902 high resolution mass spectrometer. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tennessee.

Solvents and Reagents

Anhydrous ether was used directly from a freshly-opened can. Tetrahydrofuran was distilled from lithium aluminum hydride immediately before use. Anhydrous ethanol and methanol were prepared by distilling from magnesium turnings and stored over 3 Å molecular sieves (Ventron-Alfa Products). Potassium carbonate was used for drying organic solvents (unless otherwise stated).

Obtained from the Aldrich Chemical Company were cyanogen bromide and cyclohexane-1,3-dione. These were used without further purification.

Alkaloid Modifications

O,O-Diacetyllycorine

Lycorine (1.1 g) was added to a mixture of 5.5 ml of acetic anhydride and 5.5 ml of pyridine and stirred for two days. The solvents were removed in vacuo at 50°C. The residue was recrystallized from ethanol to give .92 g (84.7%), mp 219-222°C, lit value 219-221°C (64).

O,O-Diacetyllycorine cyanobromide

O,O-diacetyllycorine (.90 g) and cyanogen bromide (.90 g) were dissolved in 55 ml of chloroform containing .5 g of anhydrous potassium carbonate. The mixture was refluxed for six hours then filtered and rotovaped to dryness. The product (1.1 g) was composed of an amorphous mixture of cyanobromides.

IR spectrum (64) NMR spectrum (64)

O,O-Diacetyllycorine cyanobromide DMSO product (14)

O,O-diacetyllycorine cyanobromide (.5 g) was dissolved in 5 ml of dimethylsulfoxide containing .5 g of sodium bicarbonate. The mixture was heated with stirring to 120°C. After one hour, a vacuum pump was attached to the system and

the solvent removed by vacuum distillation. The dark brown residue was dissolved in a 2:1 mixture of chloroform and water. After shaking, the organic layer was filtered through a cotton plug and the aqueous layer extracted with more chloroform. The organic layers were combined, dried, and evaporated to dryness to give .49 g of crude aldehyde.

The aldehyde was purified on a silica gel column packed with 1:1 chloroform:benzene. The undesired, unreacted cyanobromide was eluted first with 2:1 chloroform:benzene. The aldehyde was eluted with 100% chloroform in 60% overall yield, mp 178-180°, lit value 186-187°.

Elemental Analysis ($C_{21}H_{20}N_2O_7$) requires C, 61.17; H, 4.86; N, 6.80; found C, 61.26; H, 5.12; N, 7.08.

IR Spectrum (64) NMR Spectrum (64)

UV λ_{max} 236 nm, log ε 4.3; λ_{max} 284 nm, log ε 3.6; λ_{max} 310 nm, log ε 3.7

Conversion of the aldehyde (14) to the acetal (15)

The aldehyde (14) (175 mg) was dissolved in 2.7 ml of trimethylorthoformate and .9 ml of methanol saturated with hydrogen chloride gas. The mixture was refluxed under a nitrogen atmosphere for three hours. The solvents were evaporated and the residue placed under a vacuum. The yield of amorphous solid was 195 mg (100%).

IR Spectrum (64) NMR Spectrum (64)

Lithium aluminum hydride reductions of acetal (58)

Aqueous workup Acetal (58) (2.6 g) was dissolved in 50 ml of dry tetrahydrofuran and added dropwise with stirring to 5 g of lithium aluminum hydride in 50 ml of dry tetrahydrofuran. This mixture was kept under a nitrogen atmosphere and stirred at room temperature for nine hours. The reaction mixture was refluxed for seven hours, then stirred for another three hours at room temperature. A saturated solution (125 ml) of sodium potassium tartrate was added dropwise while the solution was kept cold. The reaction mixture was transferred to a separatory funnel and the aqueous layer washed twice with fresh tetrahydrofuran. The organic layers were combined and dried over $MgSO_4$, then filtered. The solution was evaporated to dryness and chloroform added. This yellow solution contained a white solid which was filtered. The crystals were washed with methanol to remove the yellow color. The crystals were dried to yield .3 g (15%) of lycorine mp 244-245°C. The infrared spectrum of the product was identical to a reference spectrum of authentic lycorine.

Ethyl acetate work-up Acetal (58) (1.0 g) was dissolved in 20 ml of dry tetrahydrofuran and added dropwise to a solution of one gram of lithium aluminum hydride in 20 ml of tetrahydrofuran. The mixture was allowed to stir overnight then refluxed for one hour. Ethyl acetate was added

slowly in a dropwise manner until there was no foaming upon further addition. An additional ten ml of ethyl acetate was added followed by 20 ml of water. The aqueous layer was removed and washed with tetrahydrofuran and the organic layers were combined and the solution was evaporated to dryness. Addition of chloroform caused the precipitation of a white crystalline substance in 50% yield, mp 220-222°. The compound gave a positive silicotungstic acid test. Infrared and nuclear magnetic resonance spectra indicated that the cyano and acetate groups were no longer present but that the acetal was intact and that an ethyl group was present.

IR Figure 15 NMR Figure 15

UV λ_{max} 287 nm, log ε 3.96; λ_{max} 237 nm, log ε 4.12

M.S. ($C_{19}H_{24}NO_6$) (P-CH_3) calculated 362.16036

measured 362.160882

Reactions of N-ethylacetal (59)

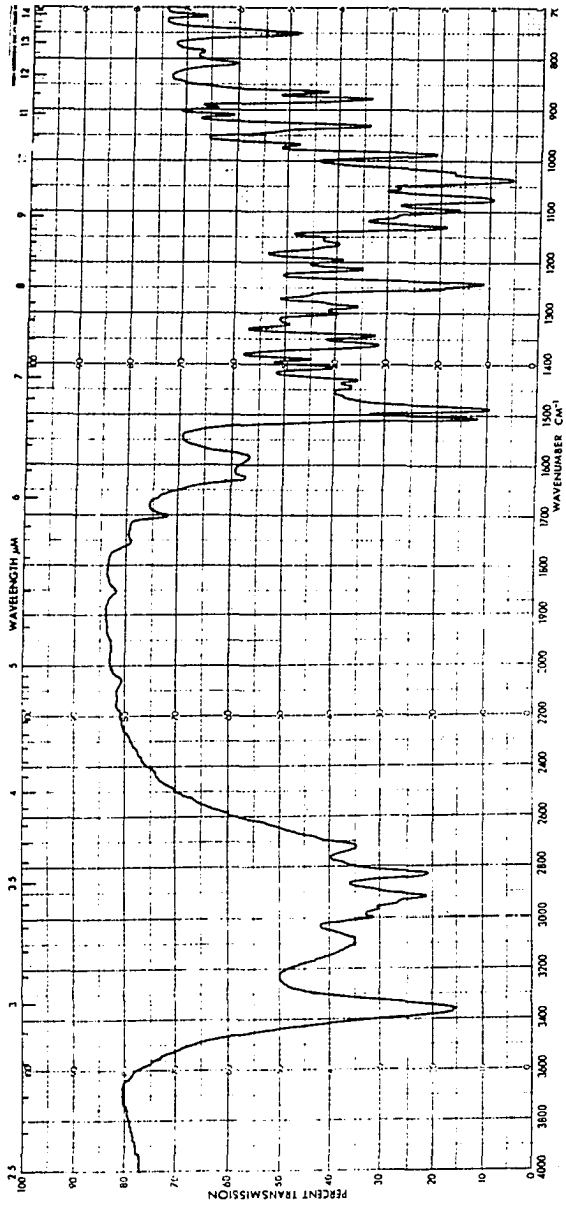
Acetylation The N-ethylacetal (59) (25 mg) was acetylated in acetic anhydride and pyridine to give a diacetate.

IR Figure 16

UV λ_{max} 286 nm, log ε 3.94; λ_{max} 238 nm, log ε 4.07

Hydrolysis of the diacetate The diacetate was dissolved in 3 ml of 10% HCl and warmed on a steam bath. After 10 min the solution was made basic with sodium bicarbonate

Figure 15. IR and NMR spectra of N-ethylacetal (59) from lithium aluminum hydride reduction of (58)


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION

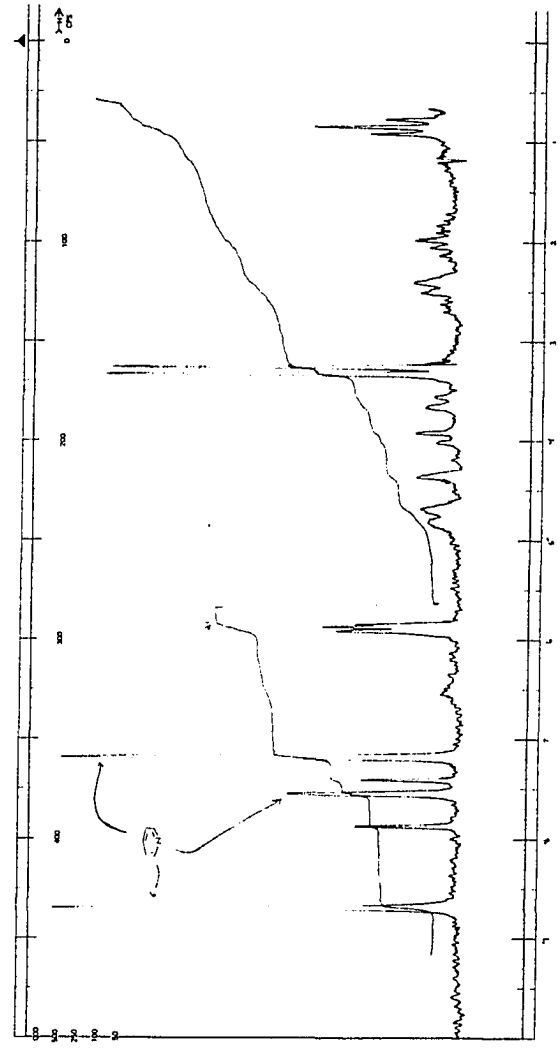
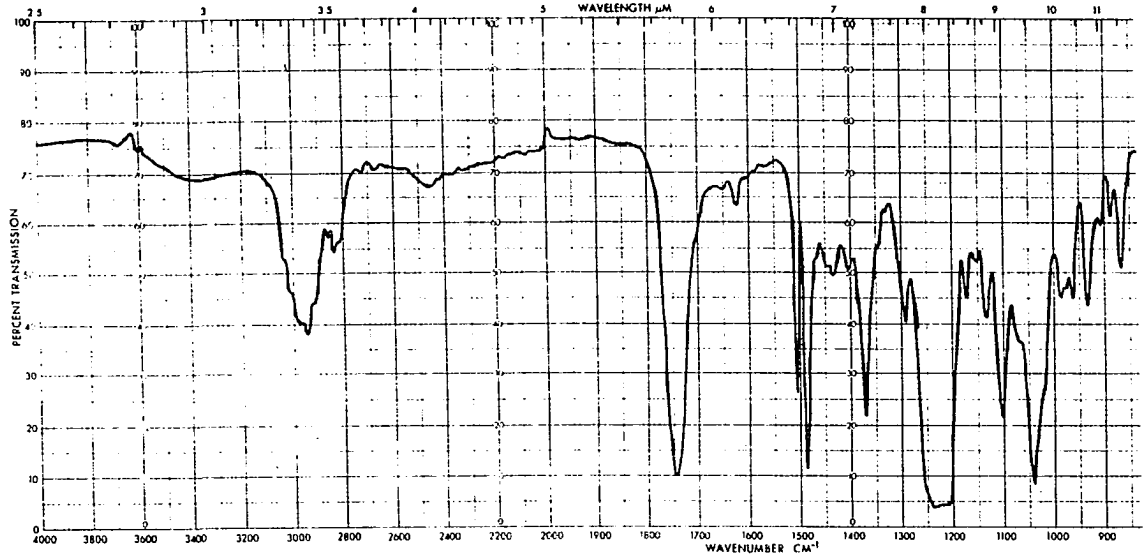
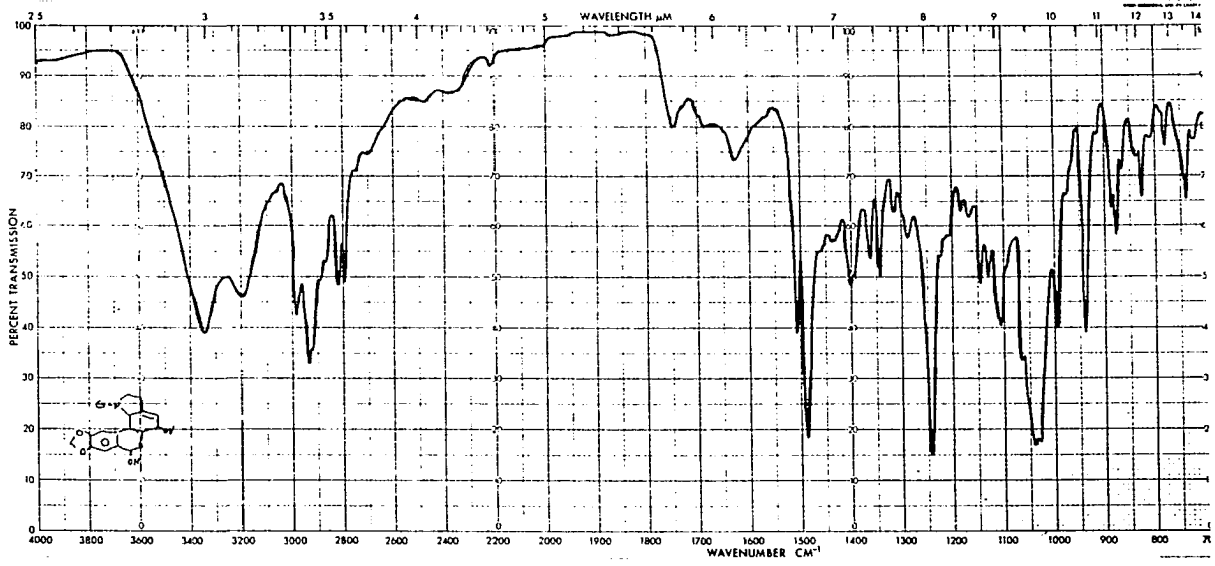


Figure 16. IR spectrum of diacetate of N-ethylacetal (59) and IR spectrum of hemiacetal (60) from hydrolysis of 59


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

and extracted with chloroform. Spectral evidence showed the product to be an aromatic aldehyde.

IR Figure 17 NMR Figure 17

UV λ_{max} 320 nm, log ε 3.84; λ_{max} 284 nm, log ε 3.88

Hydrolysis of acetal (59) N-Ethylacetal (59) (62 mg) was dissolved in 2 ml of 10% HCl. After 10 min the solution was basified with sodium bicarbonate and extracted with chloroform. The solvent was removed to give 49 mg (90%) of a hemiacetal (60, R = ethyl), mp 204-207°.

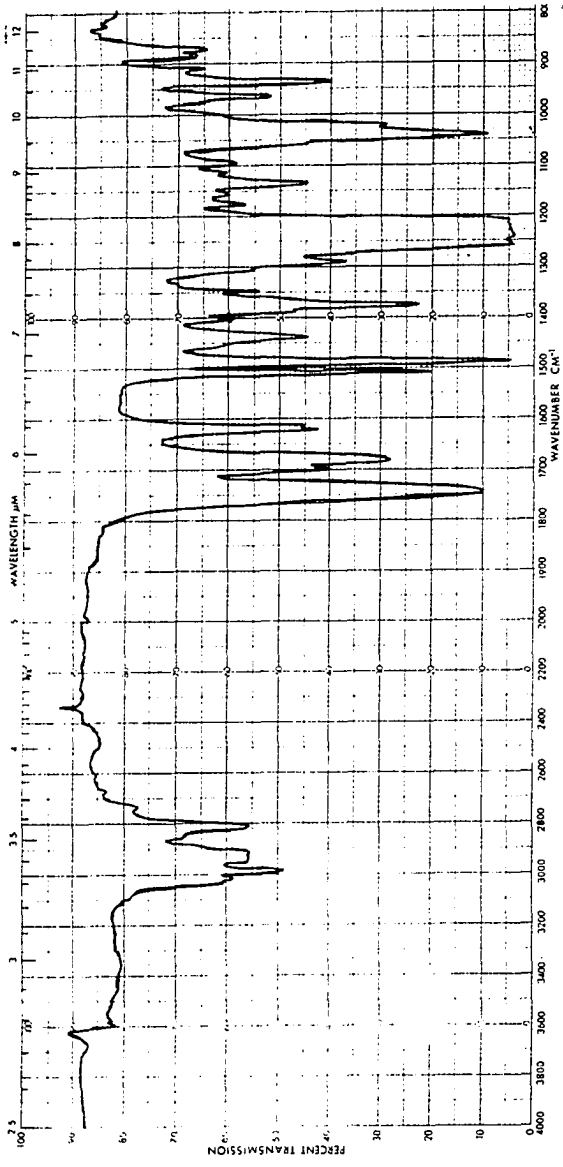
M.S. ($C_{18}H_{21}NO_5$) calculated 313.13141

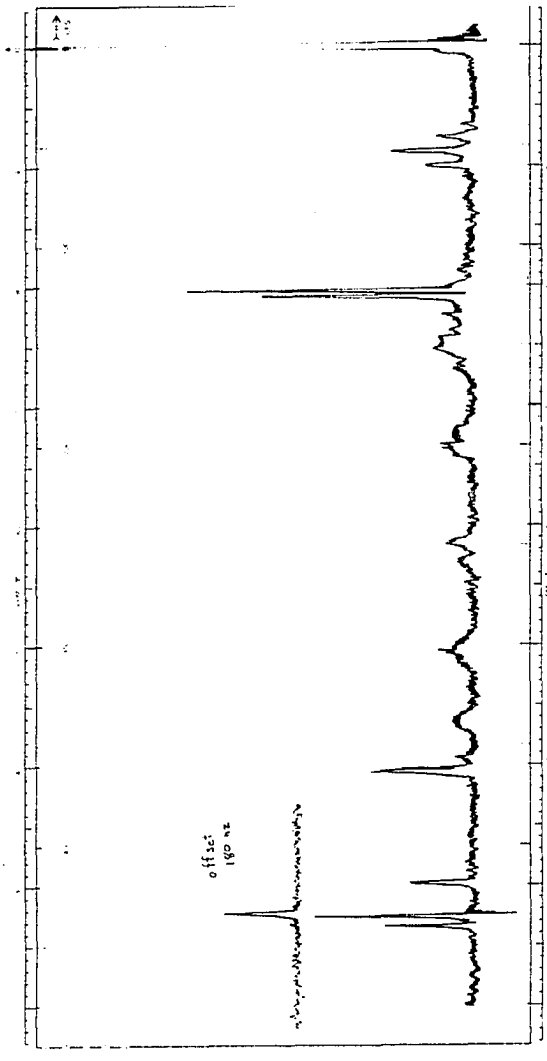
measured 313.13458 (for P-H_2O)

IR Figure 16

Alcoholysis of hemiacetal (60, R = ethyl) Hemiacetal 60, R = ethyl) (25 mg) was dissolved in 2 ml of 95% ethanol and two pellets of potassium hydroxide. This solution was allowed to stand overnight then made acidic with .5 ml of conc HCl. The mixture was diluted with distilled water and heated on a steam bath. After cooling, the solution was made basic with sodium bicarbonate and extracted into chloroform. The organic layers afforded 23 mg of material which was purified by prep scale TLC on silica gel eluting with chloroform. A similar procedure was followed using methanol instead of 95% ethanol and gave analogous results. The acetals could be hydrolyzed back to the hemiacetal with aqueous acid.

Figure 17. IR and NMR spectra of the diacetate of the aldehyde from N-ethyl-acetal (59)


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION



IR Figure 18 NMR Figure 18

Oxidation of hemiacetal (60, R = ethyl) Hemiacetal (60, R = ethyl) (20 mg) was dissolved in 10 ml of chloroform containing 100 mg of activated manganese dioxide. After stirring overnight, the solution was filtered. The infrared spectrum indicated a mixture of conjugated lactone and conjugated ketone. The infrared spectrum showed a lactone 1730 cm^{-1} and an enone 1680 cm^{-1}.

Reaction of aldehyde 14 with methanolic potassium carbonate

53 mg of cyanoaldehyde (14) was dissolved in 2 ml of dry methanol and 55 mg of anhydrous potassium carbonate. The mixture was stirred at room temperature overnight then rotovaped dry following gravity filtration. The residue was taken up in chloroform and water and shaken. The organic layer was filtered through a plug of cotton and the chloroform removed under reduced pressure. The compound crystallized from chloroform (mp 172-178°C) and was determined to have structure 17; R = CNH(OMe).

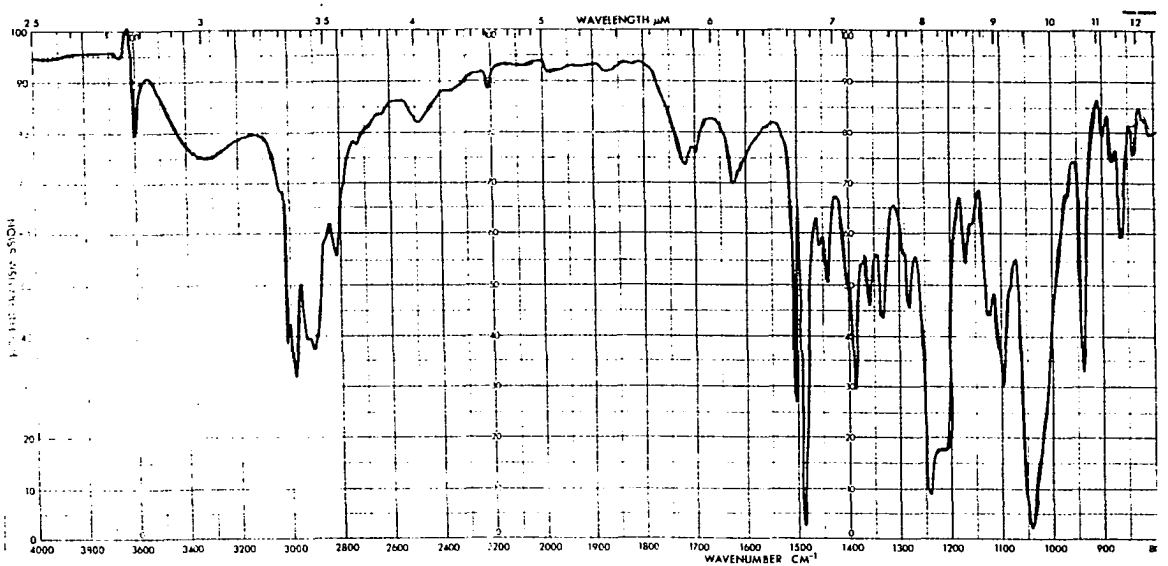
IR Figure 19

UV λ_{max} 290 nm, log ε 7.67; λ_{max} 236 nm, log ε 7.68

Haemanthamine cyanobromide

A solution of 100 mg of haemanthamine in 20 ml of methylene chloride containing 50 mg of anhydrous potassium carbonate was treated with 100 mg of cyanogen bromide. The

Figure 18. IR and NMR spectra of O-ethylacetal from hemiacetal (60, R = ethyl)


WAVELENGTH μM
WAVENUMBER CM⁻¹

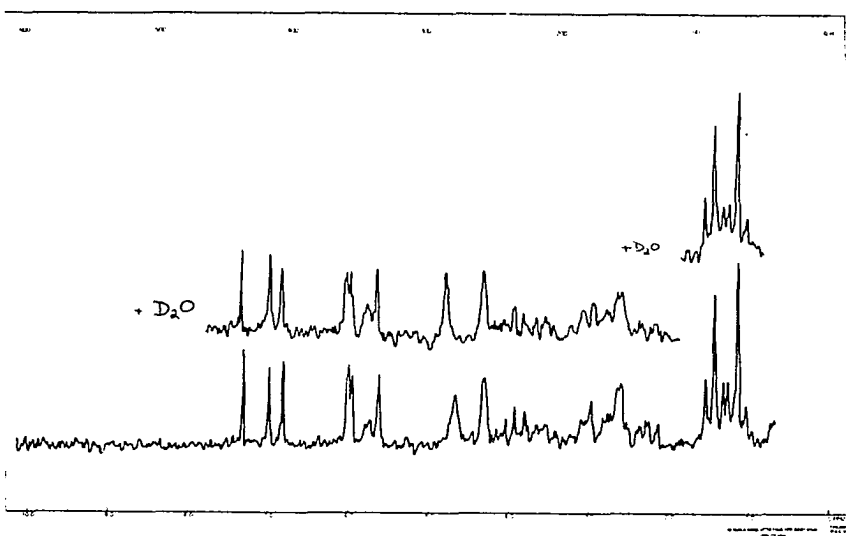
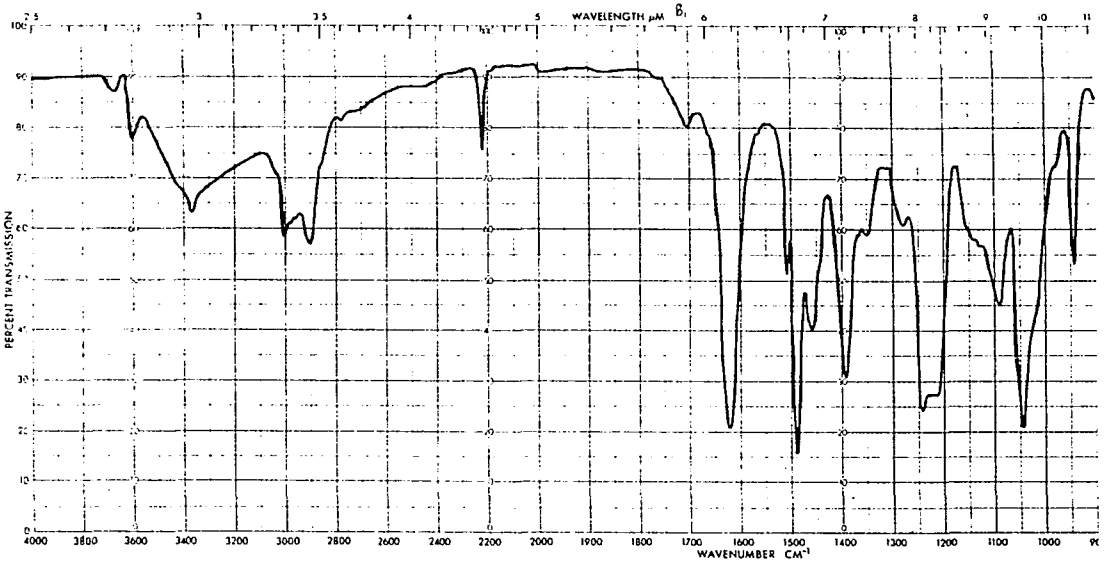

+ D₂O
+ D₂O

Figure 19. IR spectrum of imino ether (60, R = $CNH(OCH_3)$)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000

solution was stirred overnight, filtered and evaporated to dryness. Final drying by vacuum provided a fluffy solid weighing 114 mg (85%) and having one spot on a TLC plate.

IR Figure 20

Powelline cyanobromide

Powelline (500 mg) and potassium carbonate (250 mg) were suspended in 20 ml of methylene chloride. To this mixture was added, in one portion, 500 mg of cyanogen bromide. The light yellow mixture was allowed to stir at room temperature overnight. The solution was gravity filtered and evaporated to dryness. The fluffy solid was suspended in chloroform and filtered. The filtrate was discarded leaving a white solid 600 mg (88.7%) mp 188-191°C.

IR Figure 20

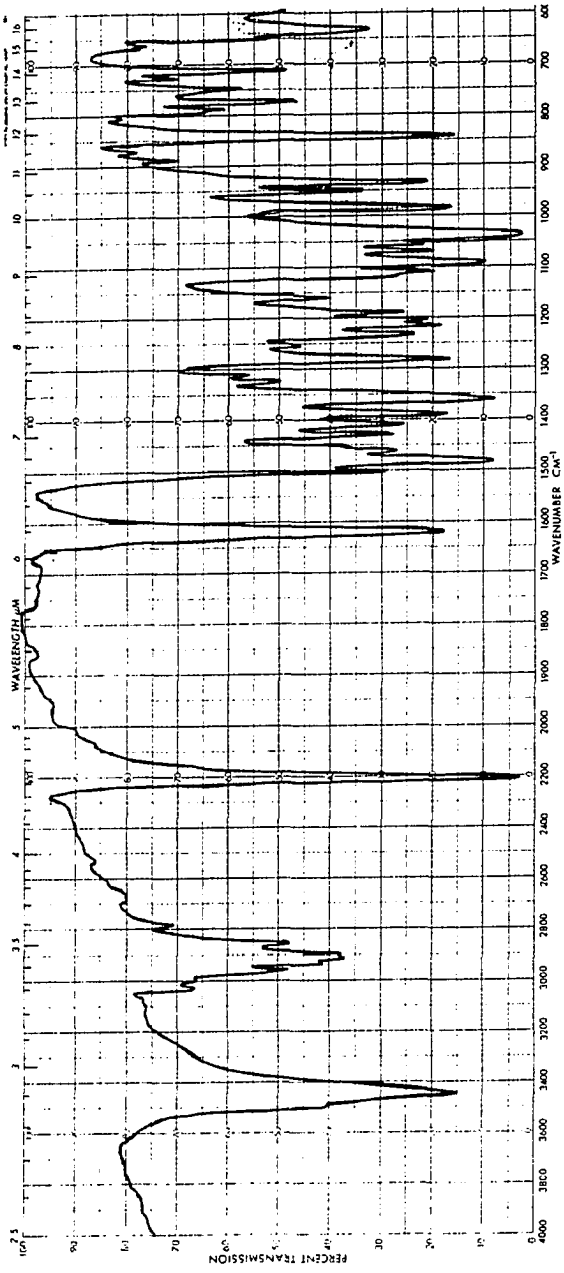
1-n-Butylpyrrolidine cyanobromide

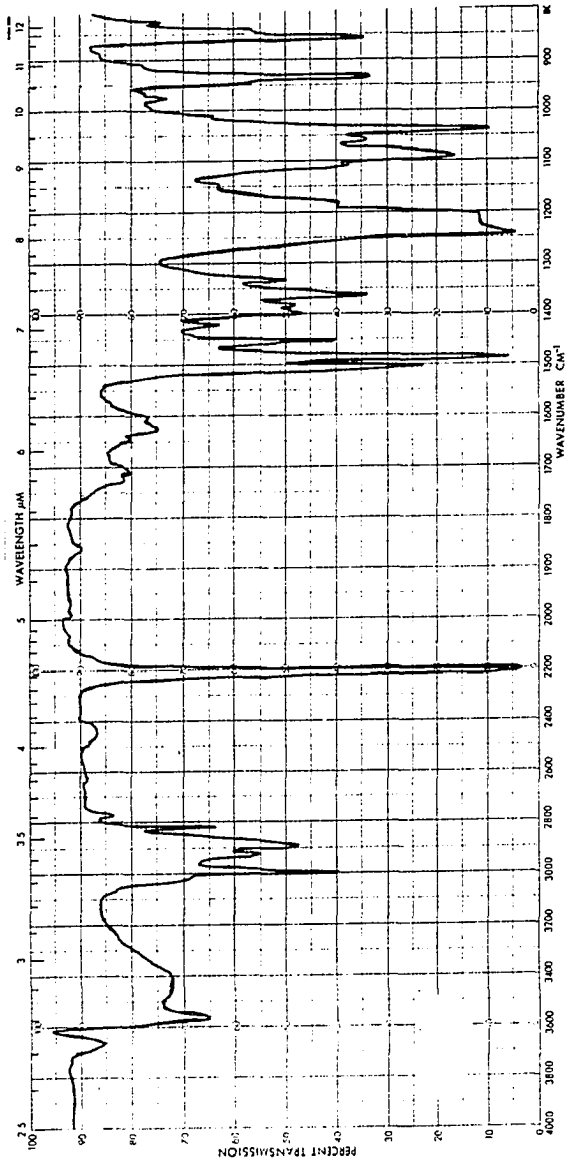
This compound was made according to Elderfield and Hageman (69) and gave an acceptable NMR spectrum.

o-Acetylpowelline cyanobromide

From powelline cyanobromide Powelline cyanobromide (4 mg) was dissolved in two milliliters of pyridine and two milliliters of acetic anhydride. The solution was stirred for six hours at room temperature then the solvents were removed in vacuo and the compound dried on a vacuum pump overnight.

Figure 20. IR spectra of powelline cyanobromide and haemanthamine cyanobromide


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION


WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION

From acetylpowelline Acetylpowelline (432 mg) was dissolved in 20 ml of methylene chloride. Potassium carbonate (216 mg) was added followed by 430 mg of cyanogen bromide. The mixture was stirred magnetically overnight then filtered and the solvent removed under reduced pressure. Placing the material on a vacuum pump afforded a puffed-up solid. Melting point and infrared spectra were identical to those of the compound prepared from powelline cyanobromide.

Reverse von Braun reactions with silver acetate

Acetylpowelline Acetylpowelline cyanobromide (27 mg) was dissolved in a mixture of 1 ml of acetic acid and .5 ml of acetic anhydride. To this solution 10 mg of silver acetate was added and the mixture stirred for seven hours. Thin layer chromatography (4 ml/1 ml/3 drops; chloroform/methanol/diethylamine) showed that all of the cyanobromide (R_f .6) had been changed into acetylpowelline (R_f .3).

Haemanthamine Haemanthamine cyanobromide (27 mg) was dissolved in a mixture of 1 ml of acetic acid, .5 ml of acetic anhydride and 10 mg of silver acetate. After 10 hours of stirring thin layer chromatography showed that all of the starting material had been transformed into haemanthamine. The mixture was poured into saturated sodium bicarbonate and extracted into chloroform. When the chloroform was removed the residue was easily recrystallized from acetone

using a seed crystal of authentic haemanthamine. The IR spectrum of the product was identical to that of haemanthamine.

1-n-Butylpyrrolidine The cyanogen bromide cleavage product of 1-n-butylpyrrolidine (550 mg) was dissolved in 10 ml of acetic acid, 10 ml of acetic anhydride and 440 mg of silver acetate. The mixture was stirred overnight then poured into sodium bicarbonate solution and made strongly basic with NaOH. This was extracted with chloroform. The organic layer was then extracted into 10% HCl, basified and re-extracted into chloroform. Removal of the solvent was accompanied by loss of most of the product but a distinct odor of the tertiary amine was observed. The cyanobromide was odorless.

Acetyllycorine cyanobromide DMSO oxidation product

The aldehyde derived from acetyllycorine cyanobromide by oxidation with dimethyl sulfoxide (14) (28 mg) was dissolved in 1 ml of acetic acid, .5 ml of acetic anhydride, and 15 mg of silver acetate. The mixture was stirred for 60 hours then poured into sodium bicarbonate solution, extracted with chloroform, dried, rotovaped and placed on a vacuum pump. The infrared spectrum of the residue was identical to the starting material.

Reduction of powelline cyanobromide

Powelline cyanobromide (315 mg) was dissolved in tetrahydrofuran and added dropwise to 1 g of lithium aluminum hydride in 25 ml of tetrahydrofuran. The mixture was refluxed for five hours then quenched with wet tetrahydrofuran followed by 5% NaOH. The granular precipitate was filtered through a Celite pad, the filtrate dried and evaporated to dryness. TLC (51.5/.25; chloroform/methanol/diethylamine) showed that the cyanobromide (R_f .7) had been converted to powelline (R_f .4).

Attempted hydrolysis of powelline cyanobromide

Powelline cyanobromide (350 mg) was dissolved in 10 ml of acetone and 10 ml of distilled water. Acetone was added dropwise until the solid was completely dissolved (a few drops). 90 mg of sodium carbonate was added and the mixture stirred magnetically and monitored by TLC. No reaction had occurred after 144 hours of stirring which included 120 hours of refluxing.

Attempted oxidation of haemanthamine cyanobromide

With dimethylsulfoxide 200 mg each of acetylhaemanthamine cyanobromide and sodium bicarbonate were dissolved in 1 ml of dimethylsulfoxide and heated to 120°C in an oil bath for one hour. The solvent was removed by rotovaping (15 mm Hg at 100°C). The residue was shaken in chloroform and water

and the organic layer was dried and rotovaped. TLC showed a mixture containing at least four components but an infrared spectrum of the mixture gave no indication of an aldehyde function.

With hexamethylenetetramine (70) Heamanthamine cyanobromide (100 mg) was dissolved in 20 ml of chloroform and 50 mg of hexamethylenetetramine added. After refluxing overnight a white precipitate appeared which was centrifuged and collected. The infrared spectrum of the compound showed that it was simply the hydrochloride of the tetramine, probably formed from HCl in the chloroform.

Attempted oxidation of powelline cyanobromide with dimethylsulfoxide

Sodium bicarbonate Acetylpowelline cyanobromide (64 mg) was heated for 1 hour at 120°C in 1 ml of dimethylsulfoxide containing 64 mg of sodium bicarbonate. The solvent was removed by gentle flaming of the flask while on the rotovap. Chloroform and water were added to the residue and the organic layer dried and evaporated. The TLC showed four components which were separated by preparatory scale TLC. None of the components had an aldehyde peak in its infrared spectrum.

Silver acetate (71) Powelline cyanobromide (100 mg) was dissolved in 7 ml of dimethylsulfoxide containing 50 mg

of silver acetate. The solution turned dark and was stirred magnetically overnight. After 11 hours, .5 ml of triethyl amine was added and the mixture stirred for another 15 min. Diethyl ether and water were added and the mixture shaken. The ether layer was dried and evaporated to give a residue which was purified by prep scale TLC. The two major components of the mixture were proved to be the starting material and powelline by comparison of their infrared spectra.

With hexamethylenetetramine (70) 26 mg of acetylpowelline cyanobromide was dissolved in chloroform and 12 mg of hexamethyltetramine added. The mixture was refluxed overnight but no characteristic precipitate was observed.

With silver nitrate - dioxane (72) Acetylpowelline cyanobromide (30 mg) was dissolved in 2.5 ml of dioxane. To this solution was added .5 ml of a solution of 10 mg of silver nitrate, 5 drops of water and 1 ml of dioxane. The mixture was allowed to stand for two hours then filtered. The black residue was dissolved in 5 ml of dioxane and .5 ml of water containing 70 mg of KOH. This mixture was heated on a steam bath for 2 hours then cooled and poured into ice and filtered to give a black tar which was insoluble in organic solvents.

With copper nitrate (73) Acetylpowelline cyanobromide (100 mg) was added to 3 ml of water containing 60 mg of copper

(II) nitrate. Carbon dioxide gas was bubbled into the solution and the mixture heated on a steam bath. After 7 hours the mixture was cooled and extracted with chloroform. The organic layer was dried and evaporated. The infrared spectrum of the product was identical to the starting material.

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